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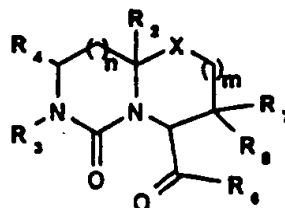
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(54) Title: **LOW MOLECULAR WEIGHT BICYCLIC-UREA TYPE THROMBIN INHIBITORS**

(57) Abstract

This invention relates to heterocyclic inhibitors of the enzyme thrombin, their preparation, and pharmaceutical compositions thereof having general formula (I), wherein X, R₂, R₃, R₄, R₆, R₇ and R₈ are as defined herein. Also, the invention relates to the use of such compounds and compositions as anticoagulants and as agents for the treatment and prophylaxis of thrombotic disorders such as venous thrombosis, pulmonary embolism and arterial thrombosis resulting in acute ischemic events such as myocardial infarction or cerebral infarction.



(I)

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**LOW MOLECULAR WEIGHT BICYCLIC-UREA TYPE
THROMBIN INHIBITORS**

FIELD OF THE INVENTION

This invention relates to compounds useful for the treatment of thrombotic disorders, and more particularly to novel heterocyclic inhibitors of the enzyme thrombin.

10 BACKGROUND

Inordinate thrombus formation on blood vessel walls precipitates acute cardiovascular disease states that are the chief cause of death in economically developed societies. Plasma proteins such as fibrinogen, proteases and cellular receptors participating in hemostasis have emerged as important factors that play a role in acute and chronic coronary disease as well as cerebral artery disease by contributing to the formation of thrombus or blood clots that effectively diminish normal blood flow and supply. Vascular
20 aberrations stemming from primary pathologic states such as hypertension, rupture of atherosclerotic plaques or denuded endothelium, activate biochemical cascades that serve to respond and repair the injury site. Thrombin is a key regulatory enzyme in the coagulation cascade; it serves a pluralistic role as both a positive and negative feedback regulator. However, in pathologic conditions the former is amplified through catalytic activation of cofactors required for thrombin generation as well as activation of factor XIII necessary for fibrin cross-linking and stabilization.

30

In addition to its direct effect on hemostasis, thrombin exerts direct effects on diverse cell types that support and

amplify pathogenesis of arterial thrombus disease. The enzyme is the strongest activator of platelets causing them to aggregate and release substances (e.g. ADP TXA₂ NE) that further propagate the thrombotic cycle. Platelets in a fibrin mesh comprise the principal framework of a white thrombus. Thrombin also exerts direct effects on endothelial cells causing release of vasoconstrictor substances and translocation of adhesion molecules that become sites for attachment of immune cells. In addition, the enzyme causes mitogenesis of smooth muscle cells and proliferation of fibroblasts. From this analysis, it is apparent that inhibition of thrombin activity constitutes a viable therapeutic approach towards the attenuation of proliferative events associated with thrombosis.

The principal endogenous neutralizing factor for thrombin activity in mammals is antithrombin III (ATIII), a circulating plasma macroglobulin having low affinity for the enzyme. Heparin exerts clinical efficacy in venous thrombosis by enhancing ATIII/thrombin binding through catalysis. However, heparin also catalyzes inhibition of other proteases in the coagulation cascade and its efficacy in platelet-dependent thrombosis is largely reduced or abrogated due to inaccessibility of thrombus-bound enzyme. Adverse side effects such as thrombocytopenia, osteoporosis and triglyceridemia have been observed following prolonged treatment with heparin.

Hirudin, derived from the glandular secretions of the leech *hirido medicinalis* is one of the high molecular weight natural anticoagulant protein inhibitors of thrombin activity (Markwardt F. Cardiovascular Drug Reviews, 10, 211, 1992). It is a biopharmaceutical that has demonstrated efficacy in

experimental and clinical thrombosis. A potential drawback to the use of Hirudin as a therapeutic agent is likely antigenicity and lack of an effective method of neutralization, especially in view of its extremely tight binding characteristics toward thrombin. The exceedingly high affinity for thrombin is unique and is attributed to a simultaneous interaction with the catalytic site as well as a distal "anion binding exosite" on the enzyme.

- 10 Thrombin activity can also be abrogated by Hirudin-like molecules such as hirulog (Maraganore, J.M. et al., Biochemistry, 29, 7095, 1990) or hirutonin peptides (DiMaio, J. et al., J. Med. Chem., 35, 3331, 1992).

Thrombin activity can also be inhibited by low molecular weight compounds that compete with fibrinogen for thrombin's catalytic site, thereby inhibiting proteolysis of that protein or other protein substrates such as the thrombin receptor. A common strategy for designing enzyme inhibitory compounds
20 relies on mimicking the specificity inherent in the primary and secondary structure of the enzyme's natural substrate. Thus, Blomback et al. first designed a thrombin inhibitor that was modeled upon the partial sequence of the fibrinogen A α chain comprising its proteolytically susceptible region (Blomback, et al., J. Clin. Lab. Invest., 24, 59, 1969). This region of fibrinogen minimally includes the residues commencing with phenylalanine:

Ala-Asp-Ser-Gly-Glu-Gly-Asp-Phe-Leu-Ala-Glu-Gly
30 -Gly-Gly-Val-Arg-Gly-Pro-Arg
 ↑ scissile bond

systematic replacement of amino acids within this region has led to optimization of the tripeptidyl inhibitory sequence exemplified by the peptide (D)-Phe-Pro-Arg which corresponds to interactions within the P_3 - P_2 - P_1 local binding sites on thrombin (Bajusz S. et al. in Peptides: Chemistry Structure and Biology: Proceedings of the Fourth American Peptide Symposium, Walter R., Meienhofer J. Eds. Ann Arbor Science Publishers Inc., Ann Arbor MI, 1975, pp. 603).

- 10 Bajusz et al. have also reported related compounds such as (D)Phe-Pro-Arg-(CO)H (GYKI-14166) and (D)MePhe-Pro-Arg-(CO)H (GYKI-14766) (Peptides-Synthesis, Structure and Function: Proceedings of the Seventh American Peptide Symposium, Rich, D.H. & Gross, E. eds., Pierce Chemical Company, 1981, pp. 417). These tripeptidyl aldehydes are effective thrombin inhibitors both *in vitro* and *in vivo*. In the case of both GYKI-14166 and GYKI-14766, the aldehyde group is presumed to contribute strongly to inhibitory activity in view of its chemical reactivity toward thrombin's catalytic Ser₁₉₅ residue,
- 20 generating a hemiacetal intermediate.

Related work in the area of thrombin inhibitory activity has exploited the basic recognition binding motif engendered by the tripeptide (D)Phe-Pro-Arg while incorporating various functional or reactive groups in the locus corresponding to the putative scissile bond (i.e. P_1 - P_1').

- In U.S. Patent 4,318,904, Shaw reports chloromethyl-ketones (PPACK) that are reactive towards Ser₁₉₅ and His₅₇. These two
- 30 residues comprise part of thrombin's catalytic triad (Bode, W. et al., EMBO Journal 8, 3467, 1989).

Other examples of thrombin inhibitors bearing the (D)Phe-Pro-Arg general motif are those incorporating COOH-terminal borooarginine variants such as boronic acids or boronates (Kettner, C. et al., J. Biol. Chem., 268, 4734, 1993).

Still other congeners of this motif are those bearing phosphonates (Wang, C-L J., Tetrahedron Letters, 33, 7667, 1992) and α -Keto esters (Iwanowicz, E.J. et al., Bioorganic and Medicinal Chemistry Letters, 12, 1607, 1992).

10

Neises, B. et al. have described a trichloromethyl ketone thrombin inhibitor (MDL-73756) and Attenburger, J.M. et al. have revealed a related difluoro alkyl amide ketone (Tetrahedron Letters, 32, 7255, 1991).

20

Maraganore et al. (European 0,333,356; WO 91/02750; U.S. 5,196,404) disclose a series of thrombin inhibitors that incorporate the D-Phe-Pro- moiety and hypothesize that this preferred structure fits well within the groove adjacent to the active site of thrombin. Variations on these inhibitors are essentially linear or cyclic peptides built upon the D-Phe-Pro moiety.

Another series of patents and patent applications have described attempts to develop effective inhibitors against thrombosis by using alpha-ketoamides and peptide aldehyde analogs (EP 0333356; WO 93/15756; WO 93/22344; WO 94/08941; WO 94/17817).

30

Still others have focused their attention on peptides, peptide derivatives, peptidic alcohols, or cyclic peptides as anti-thrombotic agents (WO 93/22344, EP 0276014; EP 0341607; EP

0291982). Others have examined amidine sulfonic acid moieties to achieve this same end (U.S. 4,781,866), while yet others have examined para or meta substituted phenylalanine derivatives (WO 92/08709; WO 92/6549).

10 A series of Mitsubishi patents and patent applications have disclosed apparently effective argininamide compounds for use as antithrombotic agents. The chemical structures described in these documents represent variations of side groups on the argininamide compound (U.S. 4,173,630; U.S. 4,097,591; CA 1,131,621; U.S. 4,096,255; U.S. 4,046,876; U.S. 4,097,472; CA 2,114,153).

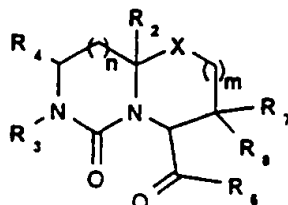
Canadian patent applications 2,076,311 and 2,055,850 disclose cyclic imino derivatives that exhibit inhibitory effects on cellular aggregation.

20 Many of the examples cited above are convergent by maintaining at least a linear acyclic tripeptidyl motif consisting of an arginyl unit whose basic side chain is required for interaction with a carboxylate group located at the base of the P₁ specificity cleft in thrombin. Two adjacent hydrophobic groups provide additional binding through favourable Van der Waals interactions within a contiguous hydrophobic cleft on the enzyme surface designated the P₃-P₂ site.

Accordingly, it is an object of the present invention is to provide thrombin inhibitors that display inhibitory activity towards the target enzyme, thrombin.

SUMMARY OF THE INVENTION

The present invention provides for novel compounds that display thrombin inhibitory activity as represented by formula (I):



wherein:

X is selected from CH-R₅, O, S, SO, SO₂ and NR₅, wherein R₅ is hydrogen, C₁₋₆ alkyl optionally interrupted with 1 or 2 heteroatoms; C₆₋₁₆ aryl, C₃₋₇ cycloalkyl or heterocyclic ring or a hydrophobic group;

R₂ is selected from H, NH₂ and C₁₋₆ alkyl optionally substituted with C₆ aryl, a 6 member heterocycle or a C₃₋₇ cycloalkyl ring;

R₃ and R₄ are independently selected from H; NR₆R₇; C₆₋₁₆ aryl or C₃₋₇ cycloalkyl optionally substituted with C₁₋₆ alkyl; C₁₋₁₆ alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR₆R₇ or a C₆₋₁₆ aryl, heterocycle or C₃₋₇ cycloalkyl group optionally substituted with halogen, hydroxyl, C₁₋₆ alkyl; an amino acid side chain; and a hydrophobic group;

R₆ is a polar amino acid residue, arginyl moiety or an analog or derivative thereof optionally substituted with an amino acid, a peptide or a heterocycle;

R₇ and R₈ are independently hydrogen or C₁₋₆ alkyl;

m is an integer between 0 and 2; and

n is an integer between 0 and 2.

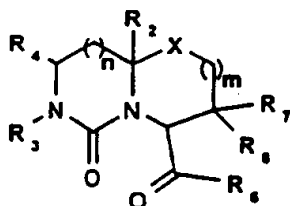
According to another aspect of the invention, there is provided pharmaceutical compositions comprising compounds of the formula (I) in combination with pharmaceutically acceptable carriers, diluents or adjuvants.

In yet another aspect, there is provided a method for the treatment or prophylaxis of thrombotic disorders in a mammal, comprising administering to said mammal an effective amount of a compound according to formula (I).

10

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds which inhibit the enzyme, thrombin. These molecules are characterized by a heterobicyclic moiety as illustrated in formula (I):



wherein X, R_1 to R_8 , m and n are as previously defined.

20 The term "hydrophobic group" (HG) as used hereinafter, refers to any group which lacks affinity for, or displaces water. Hydrophobic groups include but are not limited to C_{1-20} alkyl, C_{2-20} alkenyl (e.g. vinyl, allyl) or C_{2-20} alkynyl (e.g. propargyl) optionally interrupted by a carbonyl group, (e.g. forming an acyl group); C_{6-16} aryl, C_{3-7} cycloalkyl, C_{6-20} aralkyl, C_{6-20} cycloalkyl substituted C_{1-20} alkyl, wherein the aliphatic portion is optionally interrupted by a carbonyl group (e.g. forming an acyl group) and the ring portion is optionally substituted with C_{1-6} alkyl such as methyl ethyl or

t-butyl; or a hydrophobic amino acid side chain. Preferred hydrophobic groups include cyclohexyl, benzyl, benzoyl, phenylmethyl, phenethyl and para-t-butyl-phenylmethyl.

The term "arginyl moiety" represents an arginine amino acid residue or an analogue or derivative thereof. For example, an analogue or derivative of the natural residue may incorporate a longer or shorter methylene chain from the alpha carbon (i.e. ethylene or butylene chain); replacement of the
10 guanidino group with a hydrogen bond donating or accepting group (i.e. amino, amidino or methoxy); replacement of the methylene chain with a constrained group (i.e. an aryl, cycloalkyl or heterocyclic ring); elimination of the terminal carboxyl (i.e. des-carboxy) or hydroxyl (i.e. an aldehyde); or a combination thereof.

The term "alkyl" represents a straight or branched, saturated or unsaturated chain having a specified total number of carbon atoms.

20

The term "aromatic" or "aryl" represents an unsaturated carbocyclic ring(s) of 6 to 16 carbon atoms which is optionally mono- or di-substituted with OH, SH, amino (i.e. NR_6R_7) halogen or C_{1-6} alkyl. Aromatic rings include benzene, naphthalene, phenanthrene and anthracene. Preferred aromatic rings are benzene and naphthalene.

30

The term "cycloalkyl" represents a carbocyclic ring of 3 to 7 carbon atoms which is optionally mono- or di-substituted with OH, SH, amino (i.e. NR_6R_7) halogen or C_{1-6} alkyl. Cycloalkyl groups are generally saturated but may be partially

unsaturated and include cyclo-propyl, butyl, pentyl, hexyl and heptyl. A preferred cycloalkyl group is cyclohexyl.

The term "aralkyl" represents a substituent comprising an aryl moiety attached via an alkyl chain (e.g. benzyl, phenethyl) wherein the sum total of carbon atoms for the aryl moiety and the alkyl chain is as specified. The aryl or chain portion of the group is optionally mono- or di-substituted with OH, SH, amino (i.e. NR_6R_7), halogen or C_{1-6} alkyl

10

The term "heteroatom" as used herein represents oxygen, nitrogen or sulfur (O, N or S) as well as sulfoxyl or sulfonyl (SO or SO_2) unless otherwise indicated. It is understood that alkyl chains interrupted by one or more heteroatoms means that a carbon atom of the chain is replaced with a heteroatom having the appropriate valency. Preferably, an alkyl chain is interrupted by 0 to 4 heteroatoms and that two adjacent carbon atoms are not both replaced.

- 20 The term "heterocycle" represents a saturated or unsaturated mono- or polycyclic (i.e. bicyclic) ring incorporating 1 or more (i.e. 1-4) heteroatoms selected from N, O and S. It is understood that a heterocycle is optionally mono- or di-substituted with OH, SH, amino (i.e. NR_6R_7), halogen, CF_3 , oxo or C_{1-6} alkyl. Examples of suitable monocyclic heterocycles include but are not limited to pyridine, piperidine, pyrazine, piperazine, pyrimidine, imidazole, thiazole, oxazole, furan, pyran and thiophene. Examples of suitable bicyclic heterocycles include but are not limited to indole, quinoline, isoquinoline, purine, and carbazole.
- 30

The term "hydrophobic amino acid" represents an amino acid residue that bears an alkyl or aryl group attached to the α -carbon atom. Thus glycine, which has no such group attached to the α -carbon atom is not a hydrophobic amino acid. The alkyl or aryl group can be substituted, provided that the substituent or substituents do not detract from the overall hydrophobic character of the amino acid. Examples of hydrophobic amino acids include natural amino acid residues such as alanine; isoleucine; leucine; phenylalanine; and non-
10 naturally occurring amino acids such as those described in "The Peptides", vol. 5, 1983, Academic Press, Chapter 6 by D.C. Roberts and F. Vellaccio. Suitable non-naturally occurring amino acids include cyclohexylalanine and 1-aminocyclohexane-carboxylic.

By "amino acid side chain" is meant the substituent attached to the carbon which is α to the amino group. For example, the side chain of the amino acid alanine is a methyl group and while benzyl is the side chain for phenylalanine.
20

Preferably, X is CH-R₅, S or O wherein R₅ is preferably H or C₁₋₄ alkyl and most preferably H.

More preferably, X is S.

Preferably R₂ is H, methyl or ethyl. Most preferably, R₂ is H.

Preferably, one of R₃ or R₄ is a carboxyl group or a hydrophobic group such as a saturated or unsaturated carbocycle of 5 or 6 members optionally fused to another
30 carbocyclic group while the other is H, C₁₋₁₆ alkyl optionally substituted by NR₆R₇ or carboxy. The carboxy group or hydrophobic group may be linked via a spacer such as a C₁₋₁₆

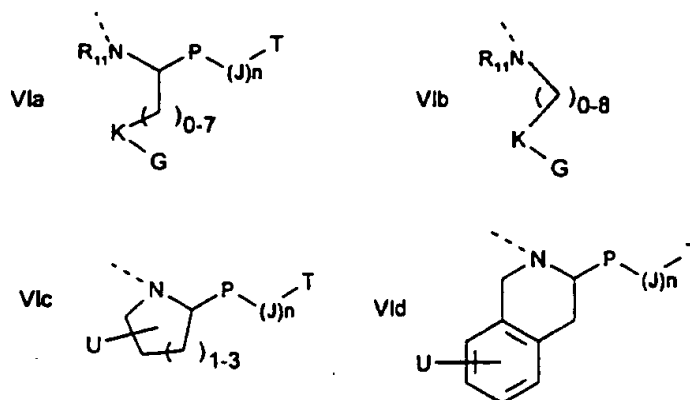
alkyl chain optionally interrupted with 1 or more (i.e. 1-4) heteroatoms, carbonyl or sulfonyl (SO₂) groups. More preferably, one of R₃ and R₄ is an optionally substituted aromatic ring such as phenyl, cyclohexyl, indole, thienyl, quinoline, tetrahydroisoquinoline, naphthyl or benzodioxolane linked via C₁₋₁₆ alkyl optionally interrupted with a heteroatom or a carbonyl while the other is H, carboxymethyl or carboxyethyl. Optional aromatic ring substituents include OH, carboxy, C₁₋₄ alkyl and halogen. In another more preferred embodiment, one of R₃ and R₄ is optionally substituted phenyl or cyclohexyl linked via a C₁₋₄ alkyl optionally interrupted with carbonyl while the other is H, carboxymethyl or carboxyethyl. In a most preferred embodiment, R₃ is benzyl, phenylethyl, phenylpropyl or cyclohexyl-methyl and R₄ is H.

Preferably R₇ and R₈ are independently hydrogen, methyl or ethyl. More preferably R₇ and R₈ are independently hydrogen or methyl. Most preferably R₇ and R₈ are both hydrogen.

20 Preferably, m is 0 or 1. More preferably, m is 0.

Preferably, n is 0 or 1. More preferably, n is 1.

In a preferred embodiment, R₆ is represented by one of formula VIa to VIId:



wherein:

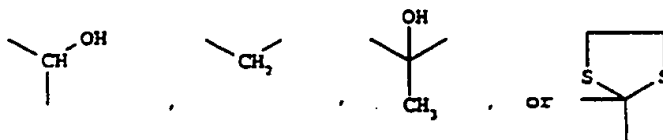
R_{11} is hydrogen or C_{1-6} alkyl;

K is a bond or $-NH-$;

G is C_{1-4} alkoxy; cyano; $-NH_2$; $-CH_2-NH_2$; $-C(NH)-NH_2$; $-NH-C(NH)-NH_2$; $-CH_2-NH-C(NH)-NH_2$; a C_6 cycloalkyl or aryl substituted with cyano, $-NH_2$, $-CH_2-NH_2$, $-C(NH)-NH_2$, $-NH-C(NH)-NH_2$ or $-CH_2-NH-C(NH)-NH_2$; or a 5 or 6 member, saturated or unsaturated heterocycle optionally substituted with cyano, $-NH_2$, $-CH_2-NH_2$, $-C(NH)-NH_2$, $-NH-C(NH)-NH_2$ or $-CH_2-NH-C(NH)-NH_2$;

U is cyano, $-NH_2$, $-C(NH)-NH_2$ or $-NH-C(NH)-NH_2$;

P is a bond, $-C(O)-$ or a bivalent group:



J is C_{1-6} alkylene optionally substituted with OH, NH_2 and C_{1-6} alkyl and optionally interrupted by a heteroatom selected from O, S and N;

n is 0 or 1; and

T is H, OH, amino, a peptide chain, C_{1-16} alkyl, C_{1-16} alkoxy, C_{6-20} aralkyl, or heterocycle optionally substituted.

20

Preferably R_{11} is H or methyl and most preferably H.

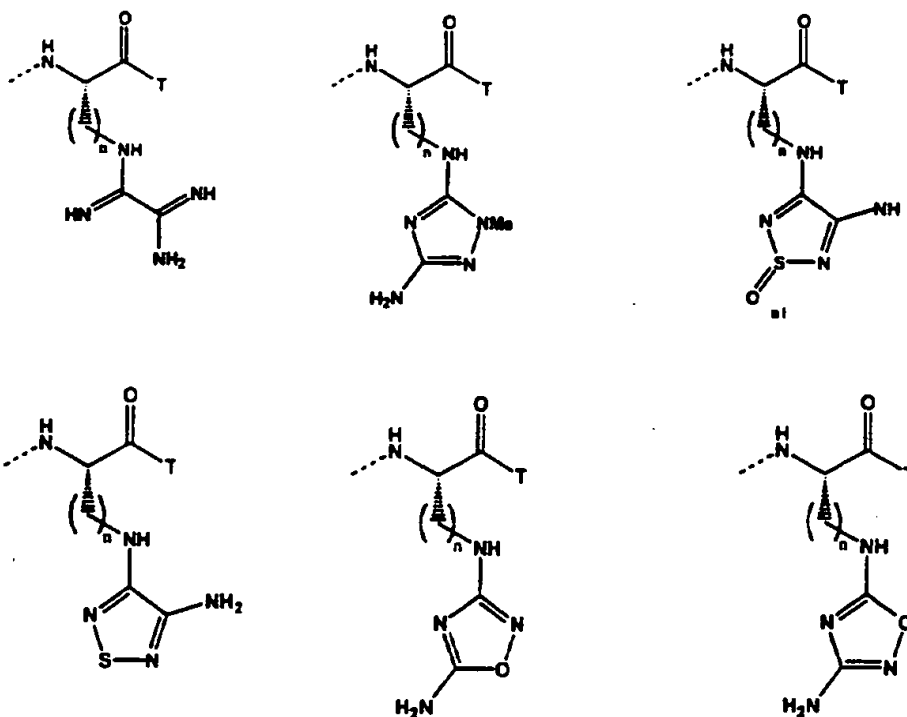
Preferably K is a bond.

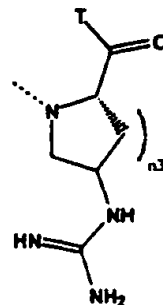
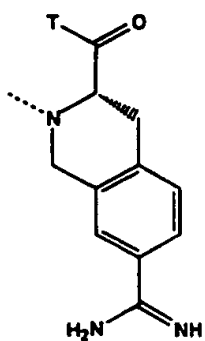
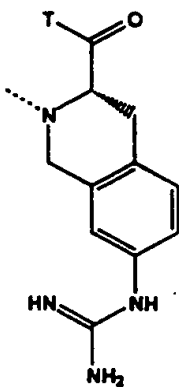
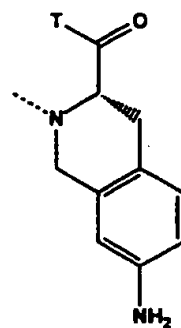
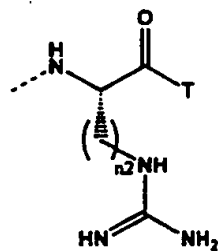
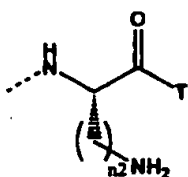
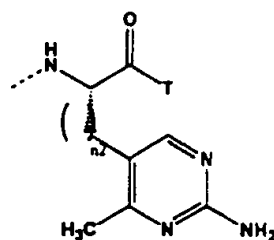
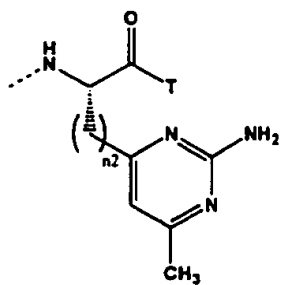
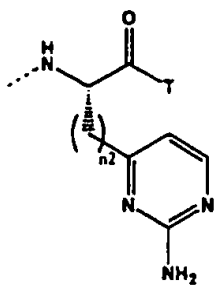
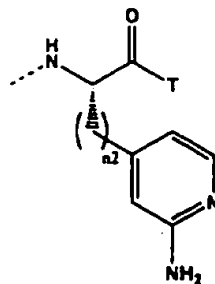
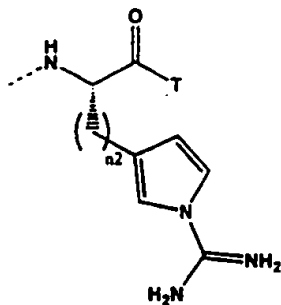
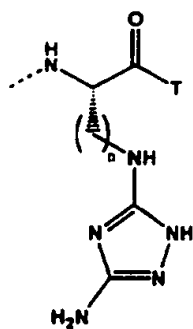
Preferably G is -NH-C(NH)-NH_2 attached via a methylene chain of 3-7 carbons or phenyl substituted with -C(NH)-NH_2 attached via a methylene chain of 0 to 3 carbons. More preferably G is -NH-C(NH)-NH_2 attached via a methylene chain of 3 atoms.

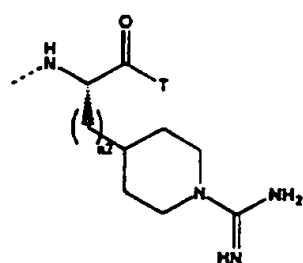
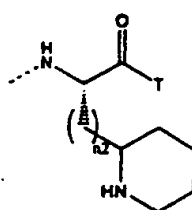
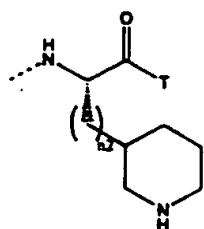
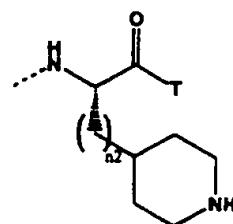
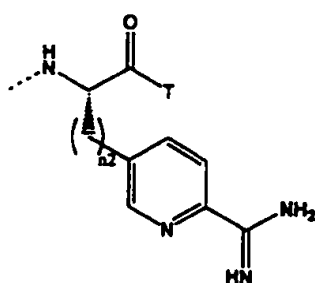
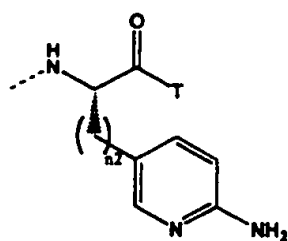
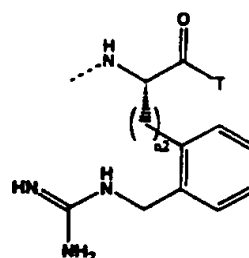
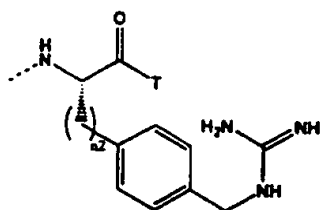
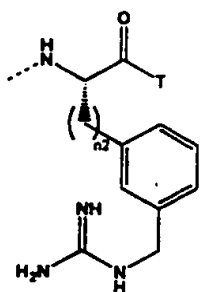
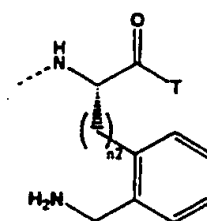
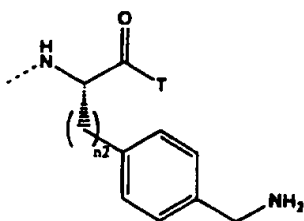
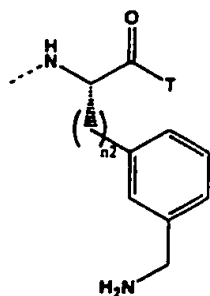
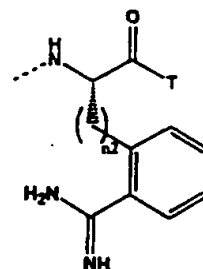
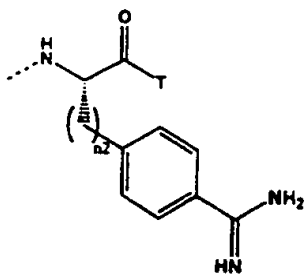
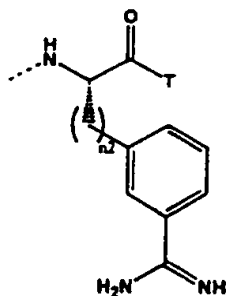
Preferably P is -C(O)- .

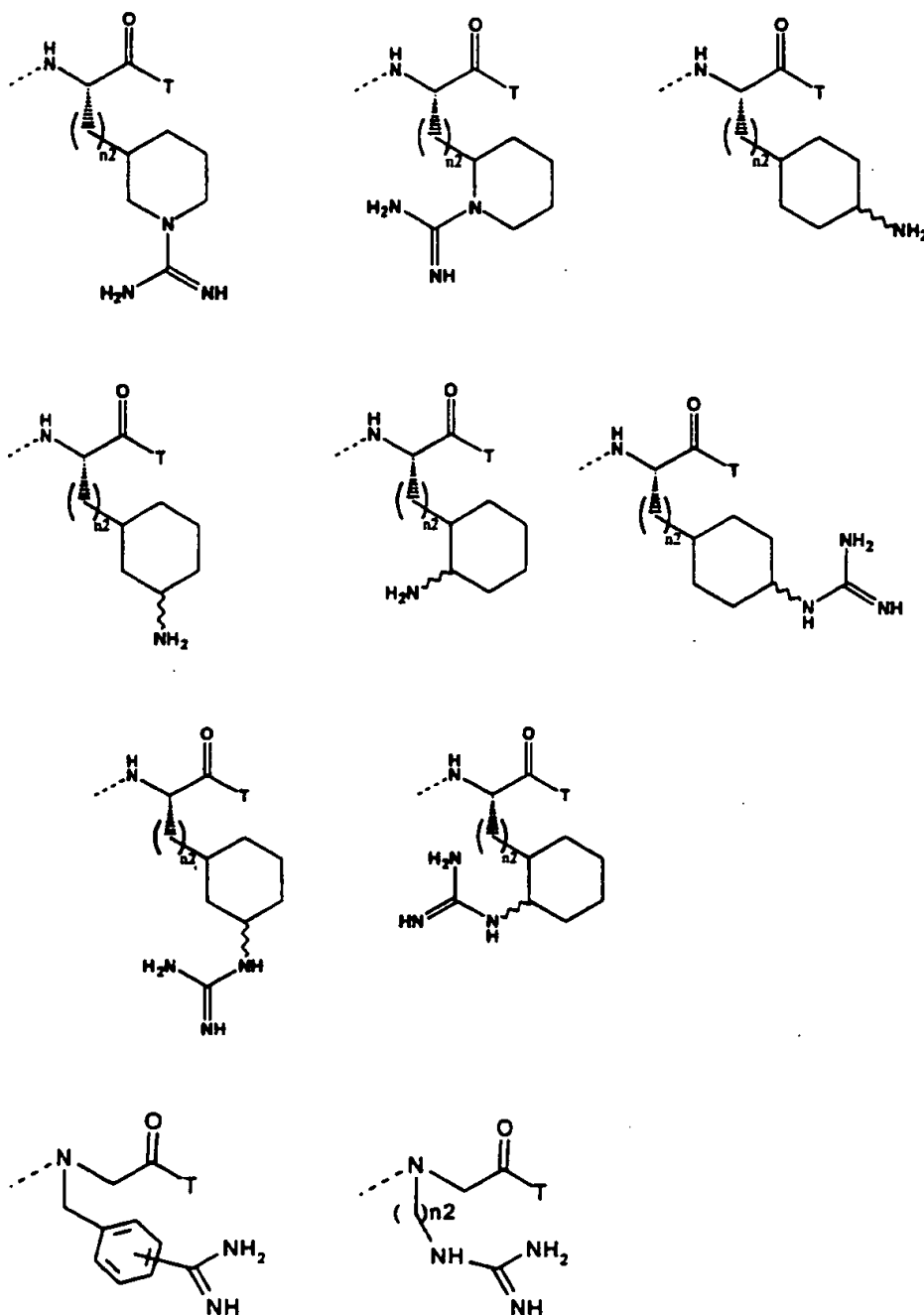
Preferably J is selected from: $\text{-CH}_2\text{-S-CH}_2\text{-CH}_2\text{-}$; $\text{-CH}_2\text{-O-CH}_2\text{-CH}_2\text{-}$; $\text{-CH}_2\text{-NH-CH}_2\text{-CH}_2\text{-}$; and a bond when n is 0. More preferably, J is a bond while n is 0.

- 10 In particular embodiments of the invention, R_6 is selected from the following amino acid derivatives prepared according to the procedures described in Bioorg. Med. Chem., 1995, 3:1145 :





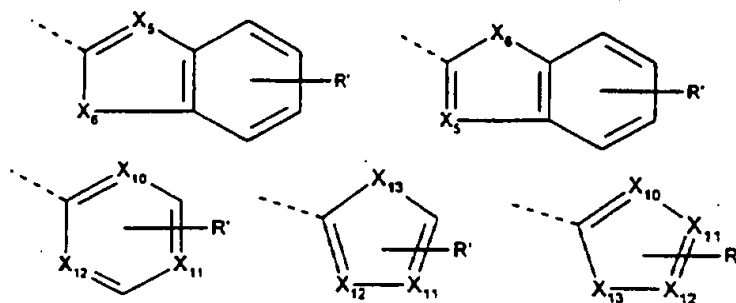




10 wherein $n=1-6$, $n_1=1-2$, $n_2=0-7$ and T is as previously defined.

In a preferred embodiment, T is a peptide of 1 to 4 amino acid residues in length and preferably fibrinogen's A or B chain or fragment or derivative thereof. In another preferred

embodiment, T is a heterocycle selected from the group consisting of:



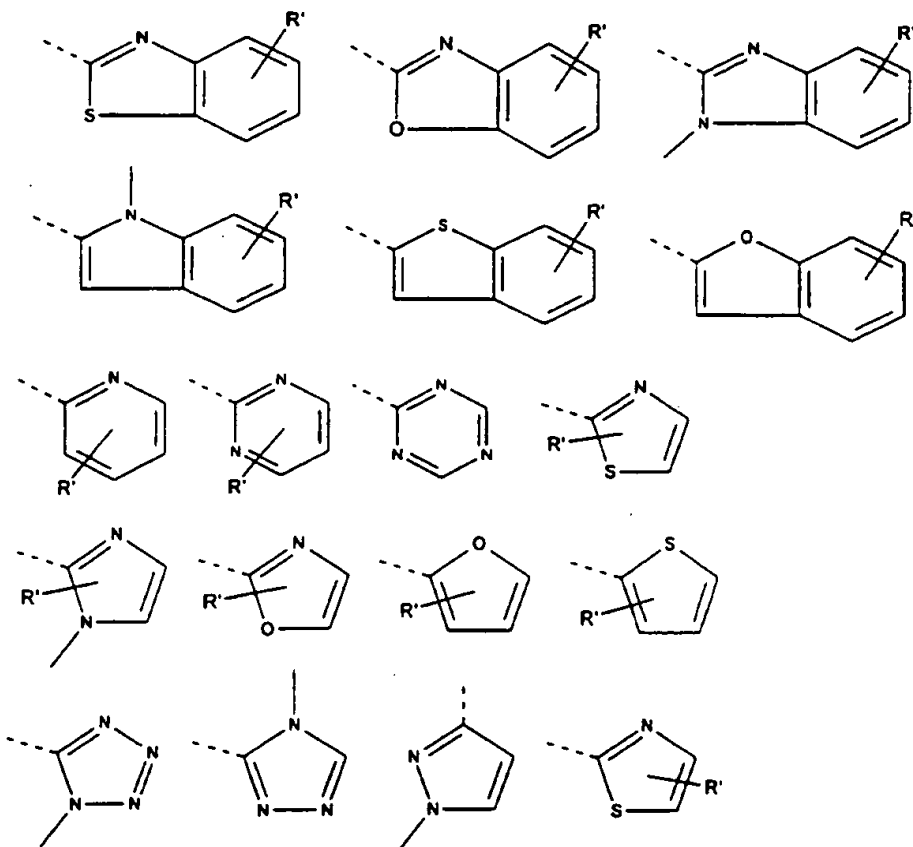
wherein

X₅, X₁₀, X₁₁ and X₁₂ are each independently selected from the group consisting of N, or C-X, where X, is hydrogen, C₁₋₄ alkyl, or C₆₋₁₆ aryl;

X₆ and X₁₃ are each independently selected from the group consisting of C, O, N, S, N-X₇, or CH-X₇;

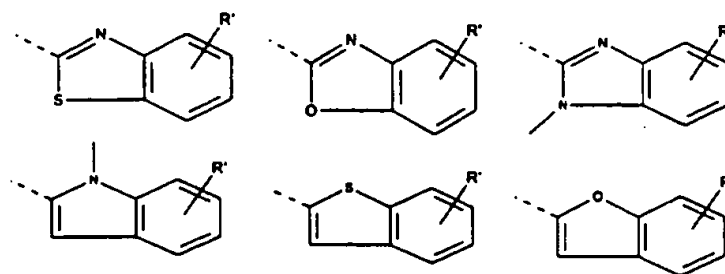
R' is hydrogen, C₁₋₁₆ alkyl optionally carboxyl substituted, carboxyl, -C₀₋₁₆ alkyl-CO₂-C₁₋₁₆ alkyl, C₆₋₂₀ aralkyl, C₃₋₇ cycloalkyl, aryl or an aromatic heterocycle.

Preferably T is selected from the group consisting of:



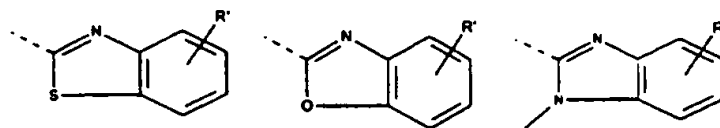
wherein R' is as defined above.

More preferably T is selected from the group consisting of:



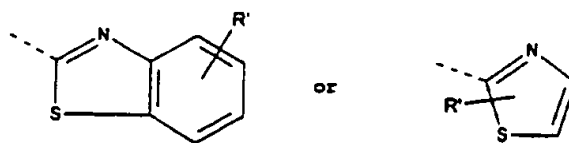
wherein R' is as defined above.

More preferably T is selected from the group consisting of:



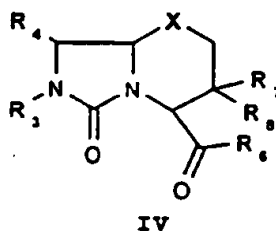
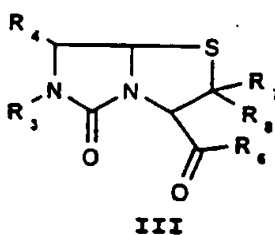
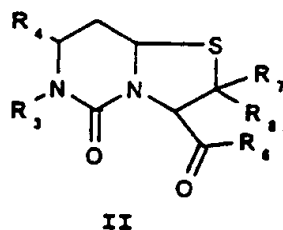
10 wherein R' is as defined above.

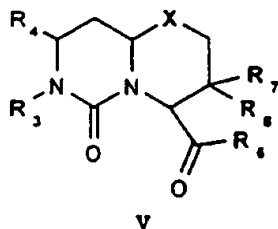
Most preferably T is



wherein R' is H or C₁₋₄ alkyl such as methyl, ethyl, propyl or butyl and most preferably wherein R' is hydrogen. In another embodiment, T is a 1,2 thiazole optionally substituted with R' and/or is attached to J at the 2, 3, 4 or 5 position of the ring.

A more preferred embodiment of the present invention is
 10 illustrated by compounds having Formulae II, III, IV, and V wherein R₃, R₄, R₆, R₇ and R₈ are as defined in each of the above embodiments.

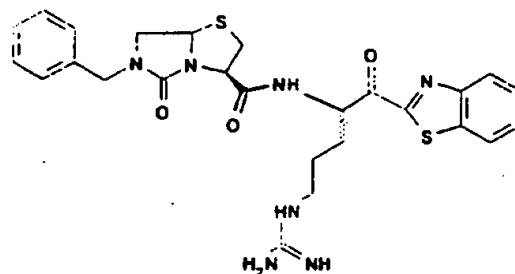




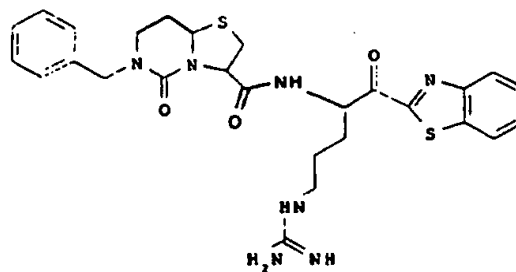
It will be appreciated by those skilled in the art that the compounds of formulae (I) to (V), depending of the substituents, may contain one or more chiral centers and thus exist in the form of many different isomers, optical isomers (i.e. enantiomers) and mixtures thereof including racemic mixtures. All such isomers, enantiomers and mixtures thereof including racemic mixtures are included within the scope of the invention.

Preferred compounds of the invention include:

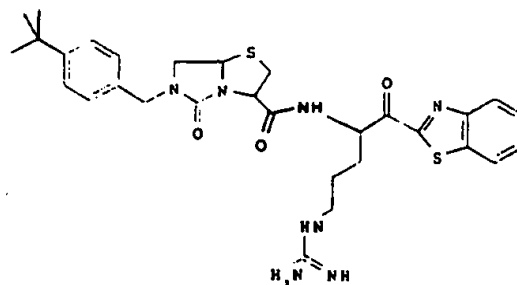
6 (3S)-6-benzyl-5-oxo-hexahydro-imidazo[5,1-b]thiazole-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide



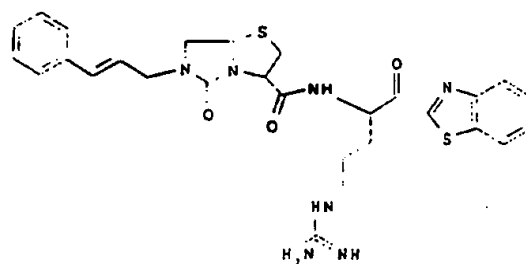
7 (S)-6-benzyl-5-oxo-hexahydro-thiazolo(3,2-c)pyrimidine-3-carboxylic acid (4-guanidino-1-(benzothiazole-2-carbonyl)-butyl)-amide



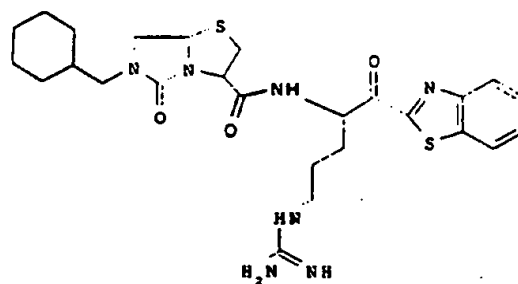
- 8 6-(para-tBu-phenylmethyl)-
5-oxo-hexahydro-
imidazo[5,1-b]thiazole-3-
carboxylic acid [1-
(benzothiazole-2-
carbonyl)-4-guanidino-
butyl]-amide



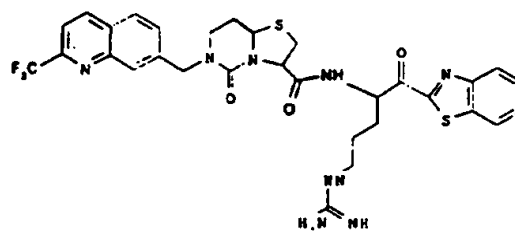
- 9 6-(3-phenyl-prop-2-enyl)-
5-oxo-hexahydro-
imidazo[5,1-b]thiazole-3-
carboxylic acid [1-
(benzothiazole-2-
carbonyl)-4-guanidino-
butyl]-amide



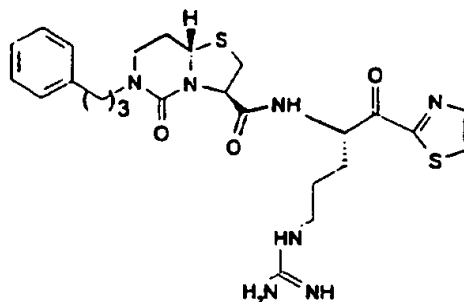
- 10 6-(cyclohexylmethyl)-5-
oxo-hexahydro-imidazo[5,1-
b]thiazole-3-carboxylic
acid [1-(benzothiazole-2-
carbonyl)-4-guanidino-
butyl]-amide



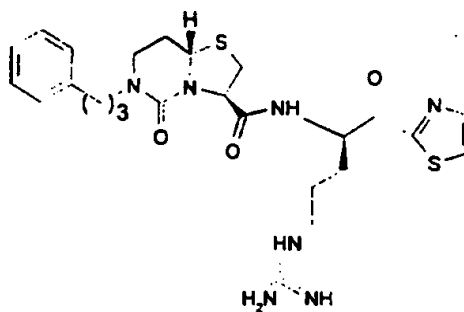
- 11 6-(2-trifluoromethyl
quinolin-7-yl)-5-oxo-
hexahydro-thiazolo(3,2-
c)pyrimidine-3-carboxylic
acid (4-guanidino-1-
(thiazole-2-carbonyl)-
butyl)-amide



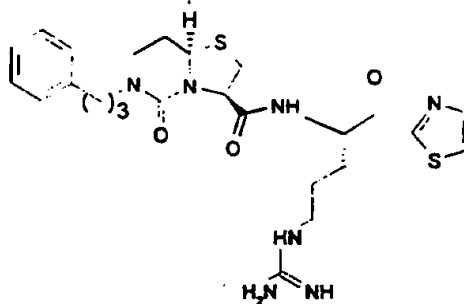
12a (3S, 9S) -6-phenylpropyl-5-oxo-hexahydro-thiazolo(3,2-c)pyrimidine-3-carboxylic acid (4-guanidino-1-(thiazole-2-carbonyl)-butyl)-amide



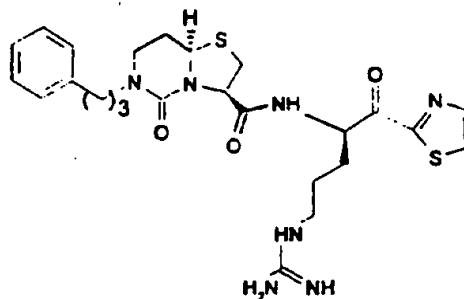
12b (3S, 9S) -6-phenylpropyl-5-oxo-hexahydro-thiazolo(3,2-c)pyrimidine-3-carboxylic acid (4-guanidino-1-(thiazole-2-carbonyl)-butyl)-amide



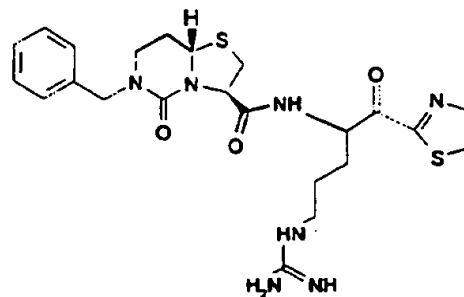
12c (3S, 9R) -6-phenylpropyl-5-oxo-hexahydro-thiazolo(3,2-c)pyrimidine-3-carboxylic acid (4-guanidino-1-(thiazole-2-carbonyl)-butyl)-amide



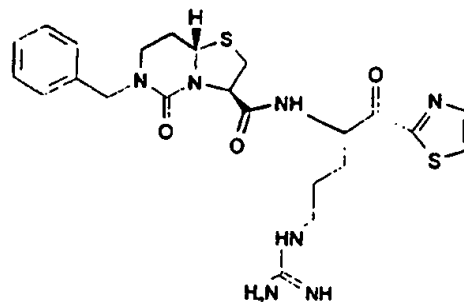
12d (3S, 9R) -6-phenylpropyl-5-oxo-hexahydro-thiazolo(3,2-c)pyrimidine-3-carboxylic acid (4-guanidino-1-(thiazole-2-carbonyl)-butyl)-amide



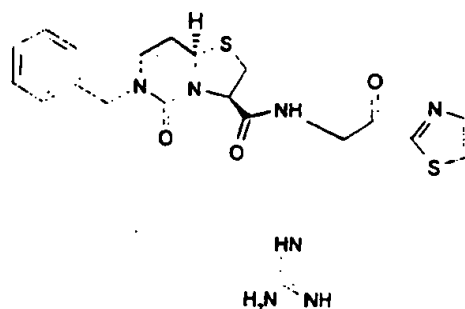
13a (3S, 9S) -6-benzyl-5-oxo-hexahydro-thiazolo(3,2-c)pyrimidine-3-carboxylic acid (4-guanidino-1-(thiazole-2-carbonyl)-butyl)-amide (fast moving isomer on HPLC)



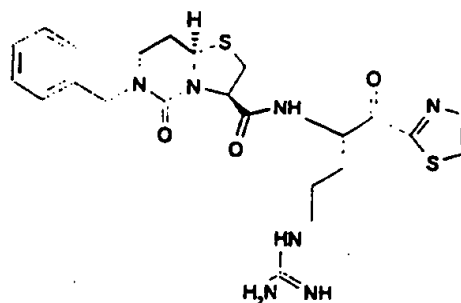
13b (3S,9S)-6-benzyl-5-oxo-hexahydro-thiazolo(3,2-c)pyrimidine-3-carboxylic acid (4-guanidino-1-(thiazole-2-carbonyl)-butyl)-amide (slow moving isomer on HPLC)



13c (3S,9R)-6-benzyl-5-oxo-hexahydro-thiazolo(3,2-c)pyrimidine-3-carboxylic acid (4-guanidino-1-(thiazole-2-carbonyl)-butyl)-amide (fast moving isomer on HPLC)



13d (3S,9R)-6-benzyl-5-oxo-hexahydro-thiazolo(3,2-c)pyrimidine-3-carboxylic acid (4-guanidino-1-(thiazole-2-carbonyl)-butyl)-amide (slow moving isomer on HPLC)



Compounds of the present invention are further characterized by their ability to inhibit the catalytic activity of thrombin, which can be demonstrated in the assay as follows. Compounds of the present invention may be prepared for assay by dissolving them in buffer to give solutions ranging in concentrations from 0 to 100 μ M. In an assay to determine the inhibitory dissociation constant, K_i , for a given compound, a chromogenic or fluorogenic substrate of thrombin would be added to a solution containing a test compound and thrombin; the resulting catalytic activity of the enzyme would be

spectrophotometrically determined. This type of assays is well known to those skilled in the art.

Accordingly, compounds of the invention may be used in the treatment and/or prophylaxis of thrombotic disorders mediated by the activity of thrombin. Such thrombotic disorders include venous thrombosis, pulmonary embolism, arterial thrombosis, myocardial infarction and cerebral infarction. Methods of treatment or prophylaxis according to the invention
10 comprise administering to a mammal, more particularly human, an effective amount of compounds of the present invention. By "effective" is meant an amount of the compound sufficient to alleviate or reduce the severity of the disorder as measured by parameters established for the particular indication i.e. blood flow (patency), clot size or density.

The compounds of the present invention may be used as anti-coagulants *in vitro* or *ex vivo* as in the case of contact activation with foreign thrombogenic surfaces such as is found
20 in tubing used in extracorporeal shunts. The compounds of the invention may also be used to coat the surface of such conduits. To this end, the compounds of the invention are obtained as lyophilized powders, redissolved in isotonic saline and added in an amount sufficient to maintain blood in an anticoagulated state.

The therapeutic agents of the present invention may be administered alone or in combination with pharmaceutically acceptable carriers, diluents or adjuvants. The proportion of
30 each carrier, diluent or adjuvant is determined by the solubility and chemical nature of the compound, the route of administration, and standard pharmaceutical practice. For

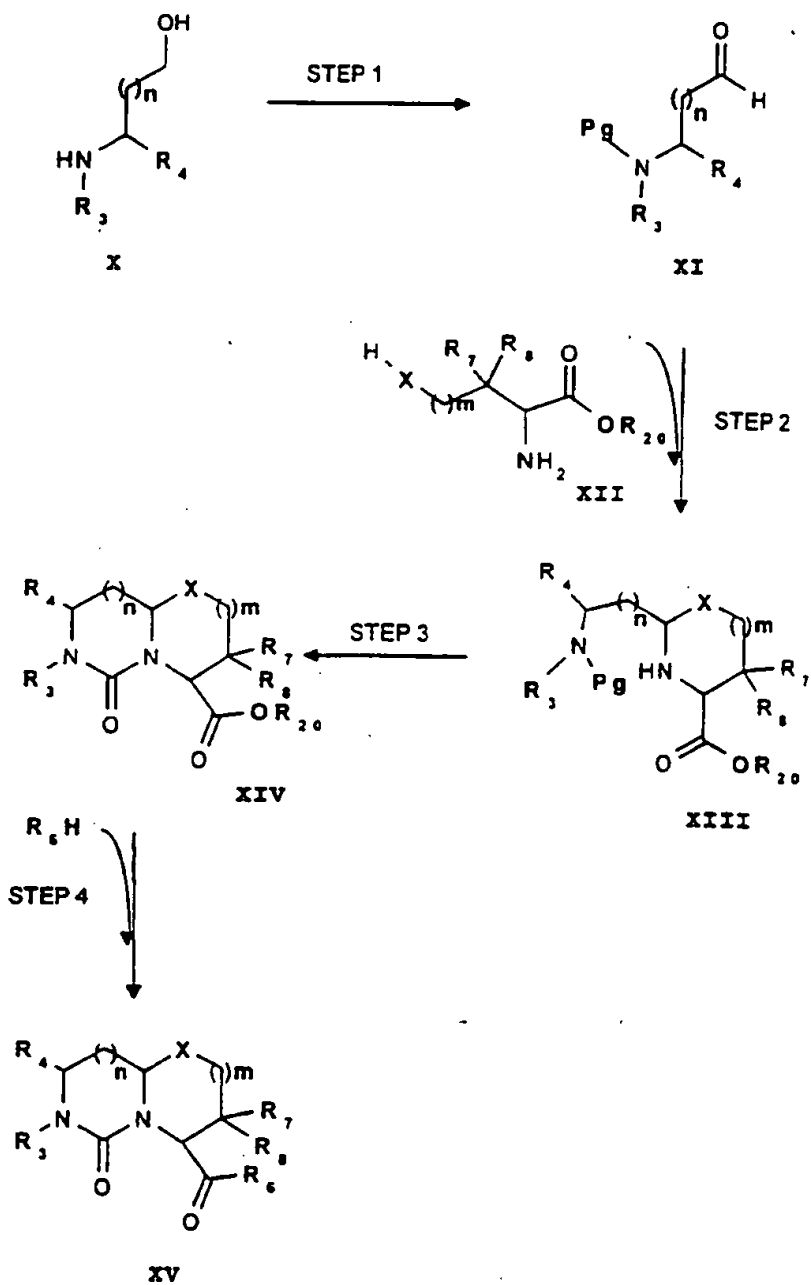
example, the compounds may be injected parenterally; this being intramuscularly, intravenously, or subcutaneously. For parenteral administration, the compound may be used in the form of sterile solutions containing other solutes, for example, sufficient saline or glucose to make the solution isotonic. The compounds may be administered orally in the form of tablets, capsules, or granules containing suitable excipients such as starch, lactose, white sugar and the like. The compounds may also be administered sublingually in the
10 form of troches or lozenges in which each active ingredient is mixed with sugar or corn syrups, flavouring agents and dyes, and then dehydrated sufficiently to make the mixture suitable for pressing into solid form. The compounds may be administered orally in the form of solutions which may contain colouring and/or flavouring agents.

Physicians will determine the dosage of the present therapeutic agents which will be most suitable. Dosages may vary with the mode of administration and the particular
20 compound chosen. In addition, the dosage may vary with the particular patient under treatment. For parenteral administration, typical dosage is about 0.1 to 500 mg/kg body weight per day, and preferably about 0.5 to 10 mg/kg body weight per day.

When the composition is administered orally, a larger quantity of the active agent will typically be required to produce the same effect as caused with a smaller quantity given parenterally.

For preparation of the compounds of this invention, various methods can be employed depending upon the particular starting materials and/or intermediates involved.

Successful preparation of these compounds is possible by way of several synthetic routes one of which is outlined below.

SCHEME 1

Wherein;

Pg is a nitrogen protecting group;

R₂₀ is a C₁₋₆ alkyl; and X, n, m, R₃, R₄, R₆, R₇, and R₈ are as defined above.

The process depicted in scheme 1 can be briefly describe as follows:

STEP 1:

The amino function of the alkylaminoalcohol of formula (X) is protected with an appropriate amino protecting group. A variety of protecting groups known for reactive functional groups and suitable protection and deprotection protocols may be found in T. Greene, Protective Groups In Organic Synthesis, (John Wiley & Sons, 1981). The appropriate protecting group to use in a particular synthetic scheme will depend on many factors, including the presence of other reactive functional groups and the reaction conditions desired for removal. The protected aminoalkylalcohol is then subjected to oxidation, using an appropriate oxidizing agent, such as a catalytic amount of tetrapropylammonium perruthenate (TPAP) along with N-methylmorpholine oxide (NMO) in an inert solvent such as dichloromethane (CH_2Cl_2) to yield to a protected amino alkyl aldehyde of formula (XI).

STEP 2

The protected amino alkyl aldehyde of formula (XI) is coupled with an amino acid alkyl ester of formula (XII) with an appropriate base such as potassium carbonate in an inert solvent such as dichloromethane to yield to a cyclic intermediate of formula (XIII).

STEP 3

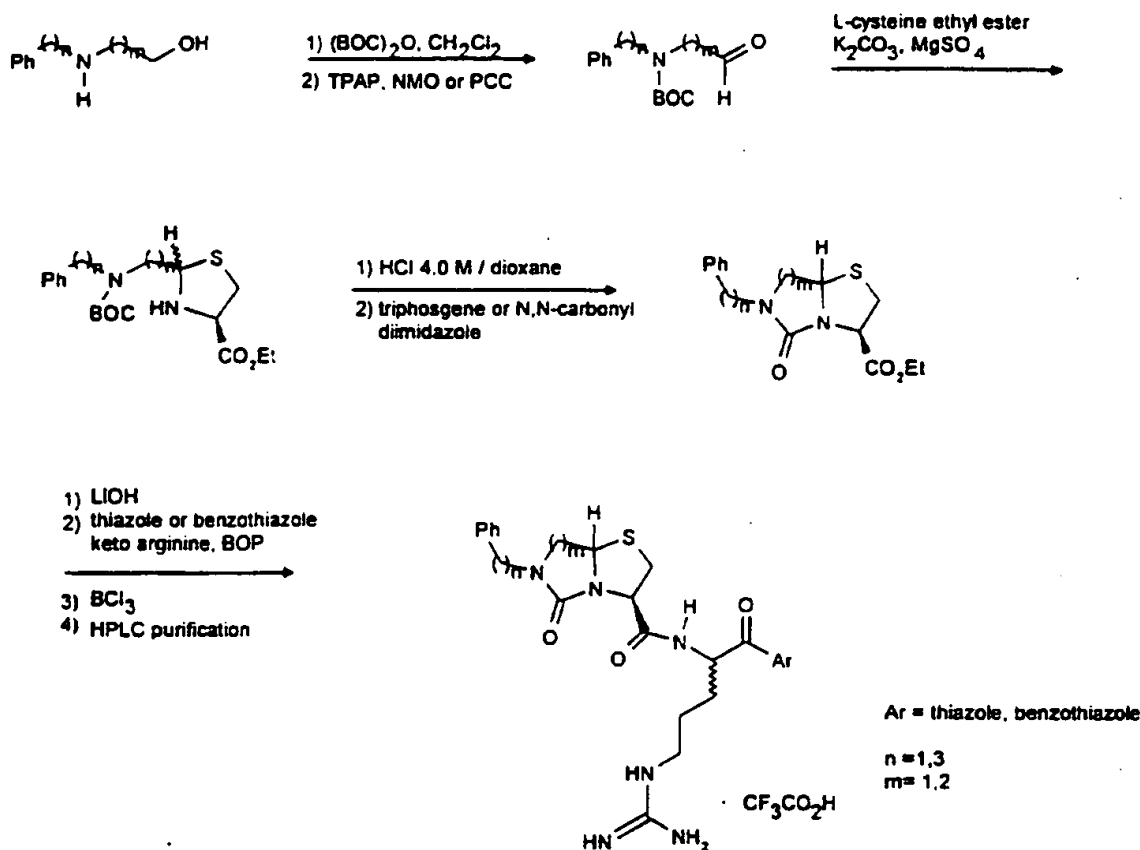
The amino protecting group of the cyclic intermediate of formula (XIII) is removed under appropriate condition and the resulting compound is then contacted with a reagent appropriate for internal ring closure such as phosgene, triphosgene or carbonyldiimidazole in an inert solvent such as tetrahydrofuran to yield to a bicyclic intermediate of formula (XIV).

STEP 4

The ester function ($-C(O)O-R_{20}$) of the bicyclic intermediate of formula (XIV) is subjected to hydrolysis using an appropriate reagent such as LiOH to yield to the free carboxylic acid. The resulting compound is then coupled to R_6H with a peptide coupling agent such as BOP in an appropriate solvent such as dimethylformamide to yield to a coupled bicyclic compound of formula (XV). Suitable conditions for peptide bond formation are well known in the art of peptide chemistry. For example see Principles of Peptide Synthesis, Bodanszky M., Springer-Verlag, Berlin, Heidelberg, New York, Tokyo 1984; and The Peptides. Analysis, Synthesis, Biology. Vol. 1, edited by Gross E., and Meienhofer J., Academic Press, New York, San Francisco, London, 1979.

In a particular embodiment wherein X is S, the following scheme 2 may be followed:

SCHEME 2



The compounds of this invention may be purified during their synthesis and/or after their preparation by standard techniques well known to the skilled artisan. One preferred purification technique is silica gel chromatography. In particular, the flash chromatographic technique may be used. However, other chromatographic methods, including HPLC, may be used for purification of the compounds. Crystallization may also be used to purify the products, as may washing procedures with appropriate organic solvents.

Where the compound of formula (I) is desired as a single isomer, it may be obtained either by resolution of the final

product or by stereospecific synthesis from isomerically pure starting material or any convenient intermediate.

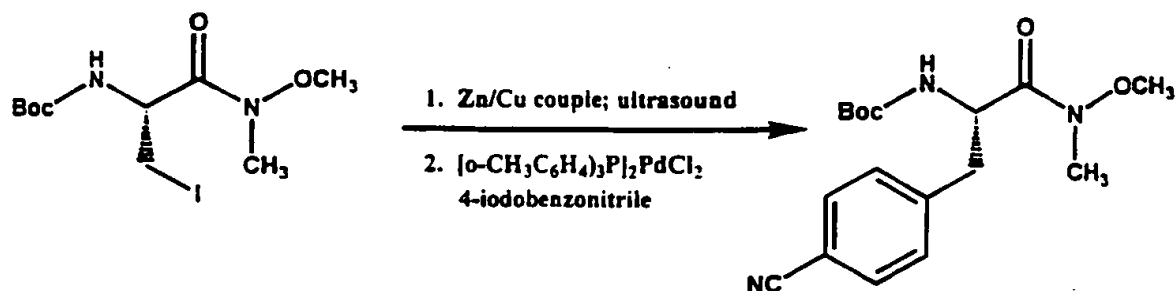
Resolution of the final product, or an intermediate or starting material therefor, may be effected by any suitable method known in the art: see for example, "Stereochemistry of Carbon Compounds", by E.L. Eliel (McGraw Hill, 1962), and "Tables of Resolving Agents", by S.H. Wilen. Resolution of the final compound can also be achieved using chiral HPLC techniques.

10

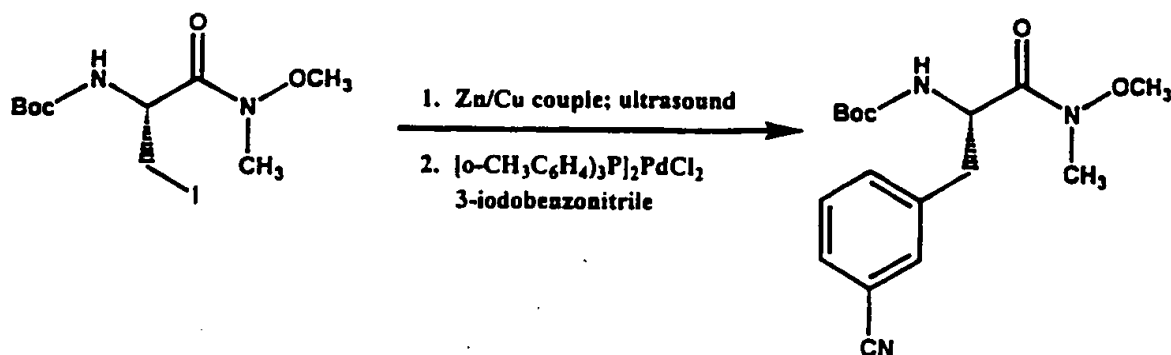
To further assist in understanding the present invention, the following non-limiting examples of such thrombin inhibitory compounds are provided. The following examples, of course, should not be construed as specifically limiting the present invention, variations presently known or later developed, which would be within the purview of one skilled in the art and considered to fall within the scope of the present invention as described herein. The preferred compounds as of the present invention can be synthesized using conventional preparative steps and recovery methods known to those skilled in the art of organic and bio-organic synthesis, while providing a new a unique combination for the overall synthesis of each compound. Preferred synthetic routes for intermediates involved in the synthesis as well as the resulting anti-thrombotic compounds of the present invention follow.

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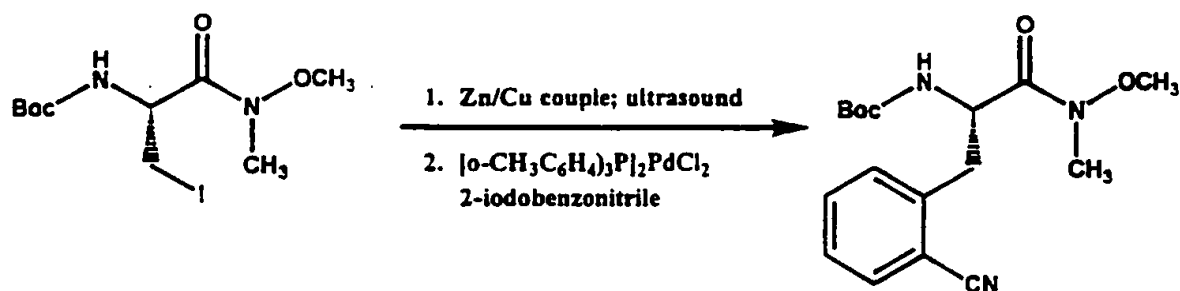
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EXAMPLE 1

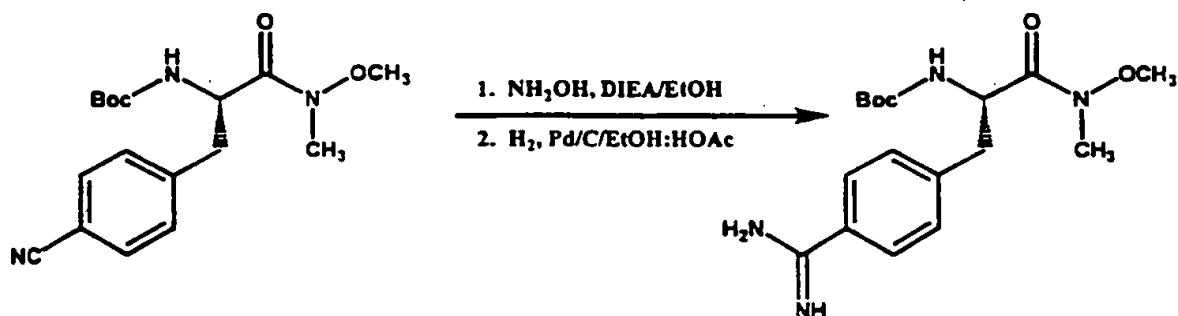
A solution of tert-butyloxycarbonyl-iodo-alanine-N,O-dimethylamide (2.68 g, 7.5 mmol) (J. Org. Chem. 1992, 57, 3397-3404) in dry benzene (30 mL), and dry N,N-dimethylacetamide (2.0 mL) was added to a dry nitrogen-purged round bottom flask charged with zinc-copper couple (0.90 g). The resulting mixture was sonicated under nitrogen until no starting material remained (as judged by TLC). Bis(tri-o-tolylphosphine)palladium dichloride (0.35 g, 0.40 mmol) was added followed by 4-iodobenzonitrile (1.72 g, 7.5 mmol). The resulting mixture was stirred under a nitrogen atmosphere with heating, allowed to cool, ethyl acetate (100 mL) was added, and the mixture filtered into a separatory funnel. Sequential washing with aqueous HCl (50 mL; 0.1N), distilled H₂O (3 x 50 mL), drying over Na₂SO₄, filtration, and concentration under reduced pressure yielded the crude product. Flash chromatography over silica gel (light petroleum-ethyl acetate gradient) afforded the purified compound.



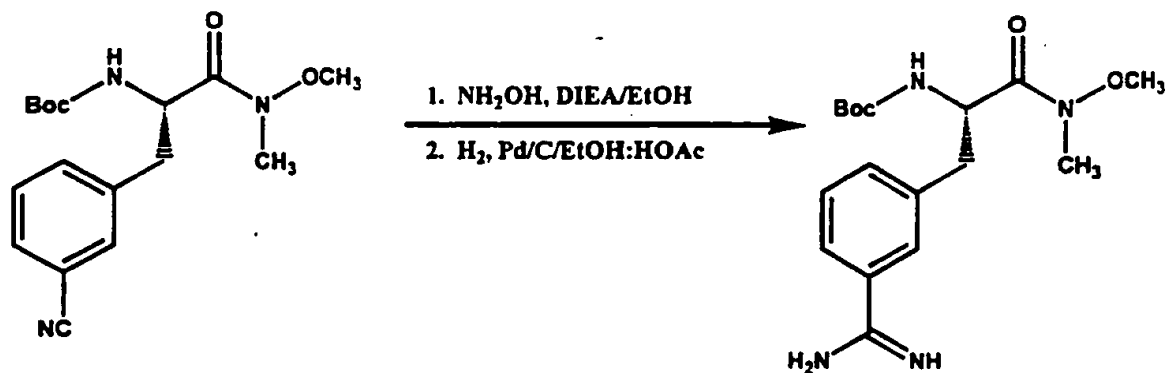
A solution of tert-butyloxycarbonyl-iodo-alanine-N,O-dimethylamide (2.68 g, 7.5 mmol) (J. Org. Chem. 1992, 57, 3397-3404) in dry benzene (30 mL), and dry N,N-dimethylacetamide (2.0 mL) was added to a dry nitrogen-purged round bottom flask charged with zinc-copper couple (0.90 g). The resulting mixture was sonicated under nitrogen until no starting material remained (as judged by TLC). Bis(tri-o-tolylphosphine)palladium dichloride (0.35 g, 0.40 mmol) was added followed by 3-iodobenzonitrile (1.72 g, 7.5 mmol). The resulting mixture was stirred under a nitrogen atmosphere with heating, allowed to cool, ethyl acetate (100 mL) was added, and the mixture filtered into a separatory funnel. Sequential washing with aqueous HCl (50 mL; 0.1N), distilled H₂O (3 x 50 mL), drying over Na₂SO₄, filtration, and concentration under reduced pressure yielded the crude product. Flash chromatography over silica gel (light petroleum-ethyl acetate gradient) afforded the purified compound.



A solution of *tert*-butyloxycarbonyl-iodo-alanine-*N*,*O*-dimethylamide (2.68 g, 7.5 mmol) (J. Org. Chem. 1992, 57, 3397-3404) in dry benzene (30 mL), and dry *N,N*-dimethylacetamide (2.0 mL) was added to a dry nitrogen-purged round bottom flask charged with zinc-copper couple (0.90 g). The resulting mixture was sonicated under nitrogen until no starting material remained (as judged by TLC). Bis(tri-*o*-tolylphosphine)palladium dichloride (0.35 g, 0.40 mmol) was added followed by 2-iodobenzonitrile (1.72 g, 7.5 mmol). The resulting mixture was stirred under a nitrogen atmosphere with heating, allowed to cool, ethyl acetate (100 mL) was added, and the mixture filtered into a separatory funnel. Sequential washing with aqueous HCl (50 mL; 0.1N), distilled H₂O (3 x 50 mL), drying over Na₂SO₄, filtration, and concentration under reduced pressure yielded the crude product. Flash chromatography over silica gel (light petroleum-ethyl acetate gradient) afforded the purified compound.

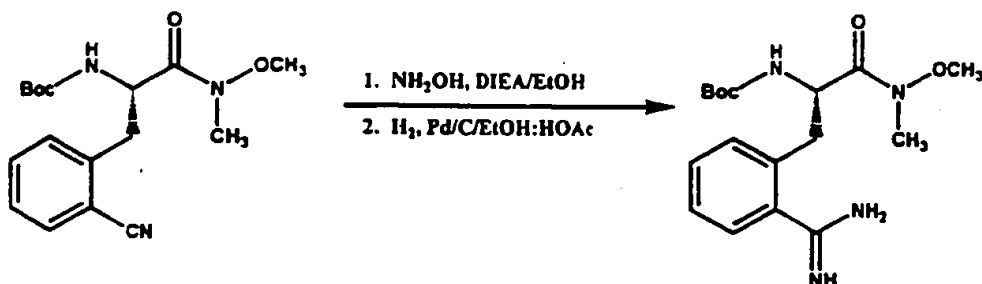


To a solution of *tert*-butyloxycarbonyl-*para*-cyano-phenylalanine-*N,O*-dimethylamide (1.33 g, 4.0 mmol) in dry ethanol (20 mL) was added hydroxylamine hydrochloride (0.416 g, 6.0 mmol), and diisopropylethylamine (1.02 mL, 6.0 mmol). The mixture was refluxed and then cooled. The precipitate was filtered, washed with cold ethanol, diisopropylether, dried with MgSO_4 , concentrated under reduced pressure, and used directly in the next step. The semi-solid was suspended in a mixture of acetic acid (20 mL), and dry ethanol (40 mL) with warming. Subsequently, Pd/C catalyst (0.30 g, 10% Pd) was added, and hydrogen was bubbled through the mixture with warming. The hydrogenation was continued until no starting material could be detected as judged by TLC. The catalyst was removed by filtration, the solution was concentrated under reduced pressure (50 mL), HCl (50 mL, 1 N) was added, and the mixture was concentrated once again to 50 mL. The solution was chilled overnight yielding the title compound.



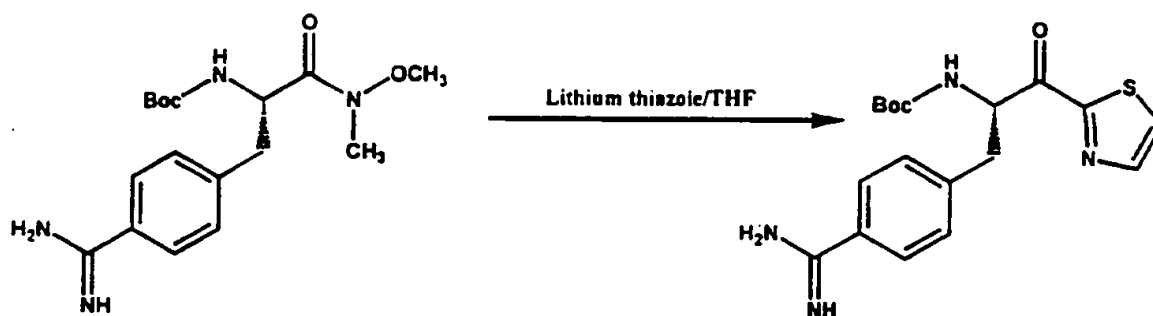
To a solution of *tert*-butyloxycarbonyl-*meta*-cyano-phenylalanine-*N,O*-dimethylamide (1.33 g, 4.0 mmol) in dry ethanol (20 mL) was added hydroxylamine hydrochloride (0.416 g, 6.0 mmol), and diisopropylethylamine (1.02 mL, 6.0 mmol). The mixture was refluxed and then cooled. The precipitate was

filtered, washed with cold ethanol, diisopropylether, dried with MgSO_4 , concentrated under reduced pressure, and used directly in the next step. The semi-solid was suspended in a mixture of acetic acid (20 mL), and dry ethanol (40 mL) with warming. Subsequently, Pd/C catalyst (0.30 g, 10% Pd) was added, and hydrogen was bubbled through the mixture with warming. The hydrogenation was continued until no starting material could be detected as judged by TLC. The catalyst was removed by filtration, the solution was concentrated under reduced pressure (50 mL), HCl (50 mL, 1 N) was added, and the mixture was concentrated once again to 50 mL. The solution was chilled overnight yielding the title compound.

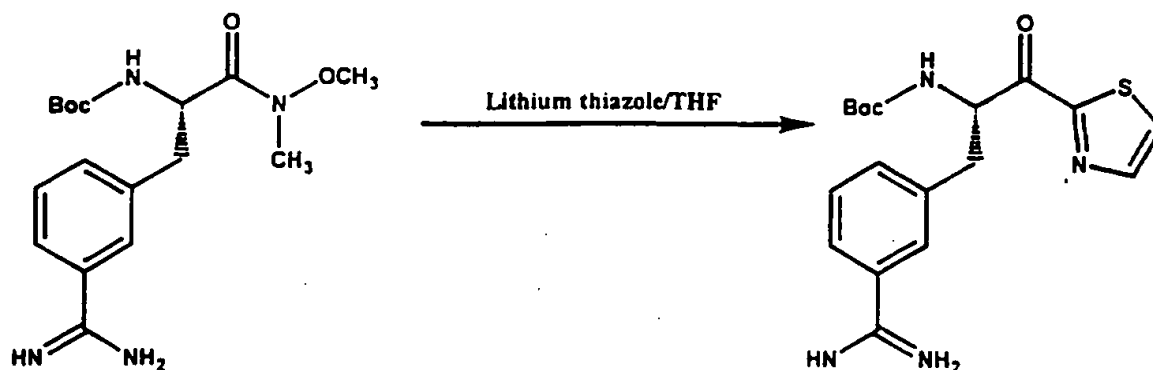


To a solution of *tert*-butyloxycarbonyl-*ortho*-cyano-phenylalanine-*N,O*-dimethylamide (1.33 g, 4.0 mmol) in dry ethanol (20 mL) was added hydroxylamine hydrochloride (0.416 g, 6.0 mmol), and diisopropylethylamine (1.02 mL, 6.0 mmol). The mixture was refluxed and then cooled. The precipitate was filtered, washed with cold ethanol, diisopropylether, dried with MgSO_4 , concentrated under reduced pressure, and used directly in the next step. The semi-solid was suspended in a mixture of acetic acid (20 mL), and dry ethanol (40 mL) with warming. Subsequently, Pd/C catalyst (0.30 g, 10% Pd) was added, and hydrogen was bubbled through the mixture with

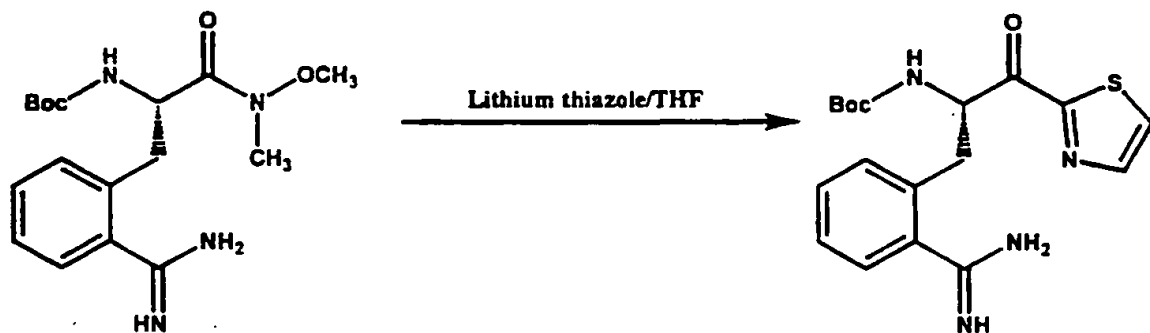
warming. The hydrogenation was continued until no starting material could be detected as judged by TLC. The catalyst was removed by filtration, the solution was concentrated under reduced pressure (50 mL), HCl (50 mL, 1 N) was added, and the mixture was concentrated once again to 50 mL. The solution was chilled overnight yielding the title compound.



To a solution of thiazole (1.28 g, 15.0 mmol) in anhydrous THF (30 mL) was added *n*-BuLi (1.6 M/hexane, 8.9 mL, 13.9 mmol) dropwise at -78° C, and the solution stirred. tert-Butyloxycarbonyl-para-amidino-phenylalanine-N,O-dimethylamide (1.15 g, 3.3 mmol) in THF (15 mL) was then added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with MgSO₄, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.

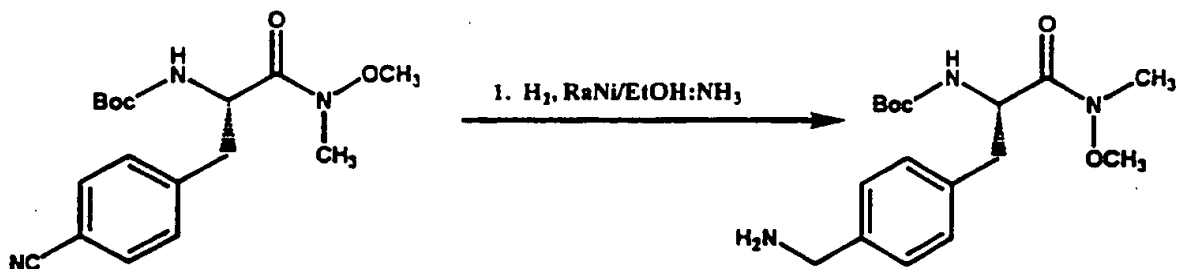


To a solution of thiazole (1.28 g, 15.0 mmol) in anhydrous THF (30 mL) was added *n*-BuLi (1.6 M/hexane, 8.9 mL, 13.9 mmol) dropwise at -78°C , and the solution stirred. *tert*-Butyloxycarbonyl-*meta*-amidino-phenylalanine-*N*,*O*-dimethylamide (1.15 g, 3.3 mmol) in THF (15 mL) was then added dropwise and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with MgSO_4 , filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.

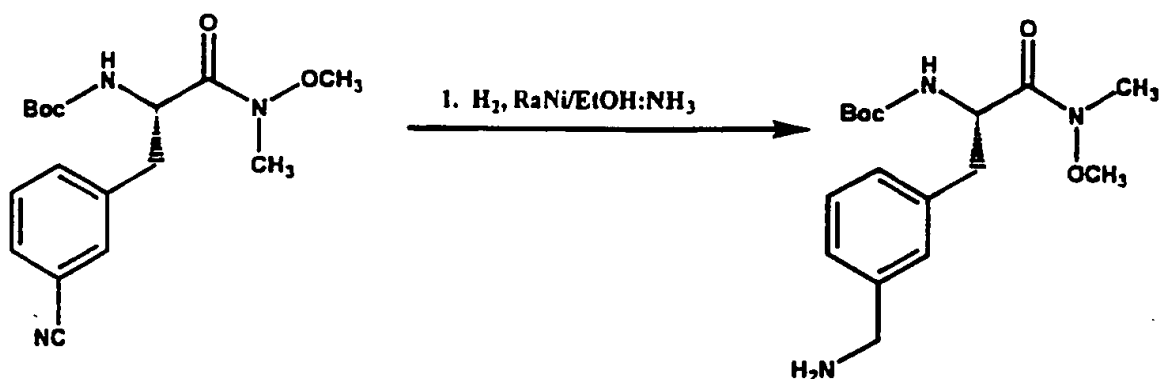


To a solution of thiazole (1.28 g, 15.0 mmol) in anhydrous THF

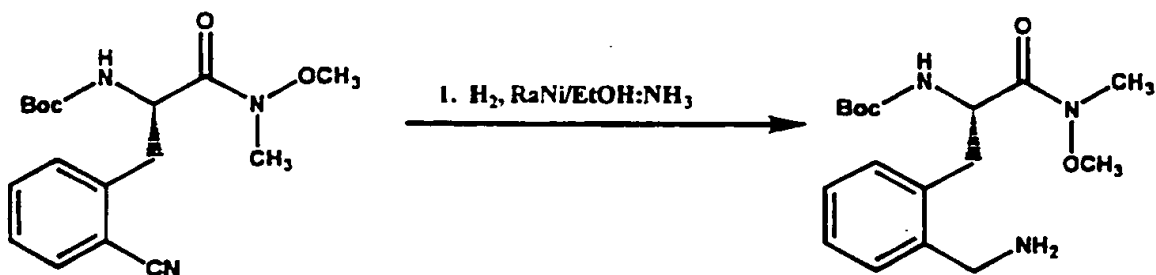
(30 mL) was added *n*-BuLi (1.6 M/hexane, 8.9 mL, 13.9 mmol) dropwise at -78°C , and the solution stirred. *tert*-Butyloxycarbonyl-*ortho*-amidino-phenylalanine-*N,O*-dimethylamide (1.15 g, 3.3 mmol) in THF (15 mL) was then added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL) and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with MgSO_4 , filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.



tert-Butyloxycarbonyl-*para*-cyano-phenylalanine-*N,O*-dimethylamide (1.33 g, 4.0 mmol) was dissolved in ethanol saturated with ammonia (30 mL), and sponge Raney Ni (100 mg) added. The solution was shaken under H_2 at room temperature (40 psi). The solution was filtered through celite, and concentrated under reduced pressure to yield a clear residue. The residue was dissolved in ethyl acetate (250 mL), and washed with 1 N NaOH (2 x 50 mL), and brine (2 x 50 mL). The solution was dried with MgSO_4 , filtered, and concentrated under reduced pressure.

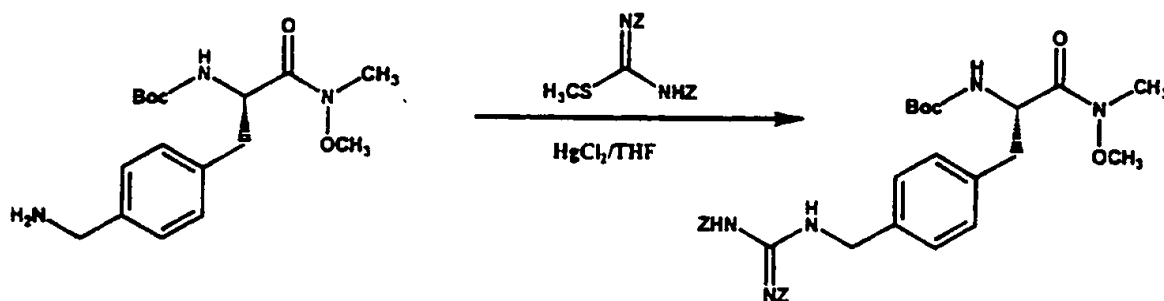


tert-Butyloxycarbonyl-*meta*-cyano-phenylalanine-N,O-dimethylamide (1.33 g, 4.0 mmol) was dissolved in ethanol saturated with ammonia (30 mL), and sponge Raney Ni (100 mg) added. The solution was shaken under H₂ at room temperature (40 psi). The solution was filtered through celite, and concentrated under reduced pressure to yield a clear residue. The residue was dissolved in ethyl acetate (250 mL), and washed with 1 N NaOH (2 x 50 mL), and brine (2 x 50 mL). The solution was dried with MgSO₄, filtered, and concentrated under reduced pressure.

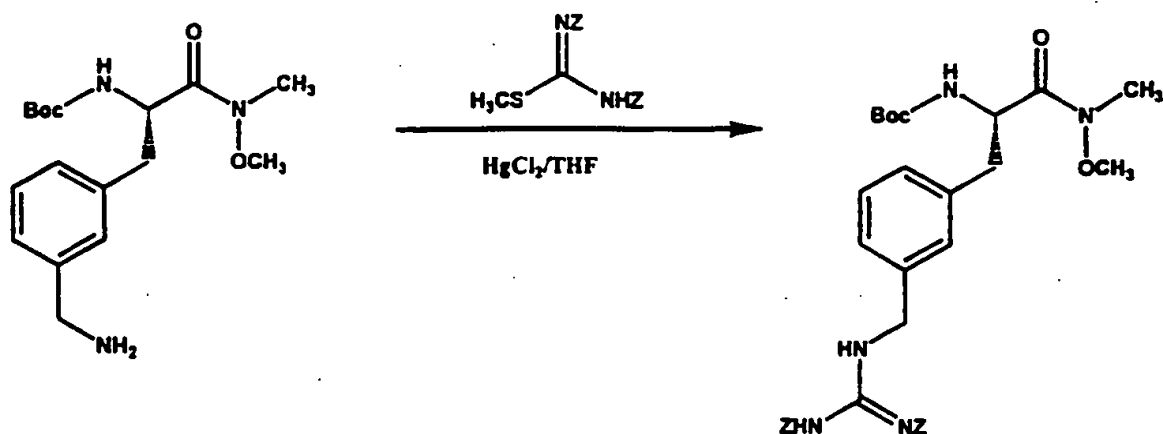


tert-Butyloxycarbonyl-*ortho*-cyano-phenylalanine-N,O-dimethylamide (1.33 g, 4.0 mmol) was dissolved in ethanol saturated with ammonia (30 mL), and sponge Raney Ni (100 mg) added. The solution was shaken under H₂ at room temperature (40 psi). The solution was filtered through celite, and concentrated under reduced pressure to yield a clear residue.

The residue was dissolved in ethyl acetate (250 mL), and washed with 1 N NaOH (2 x 50 mL), and brine (2 x 50 mL). The solution was dried with MgSO_4 , filtered, and concentrated under reduced pressure.

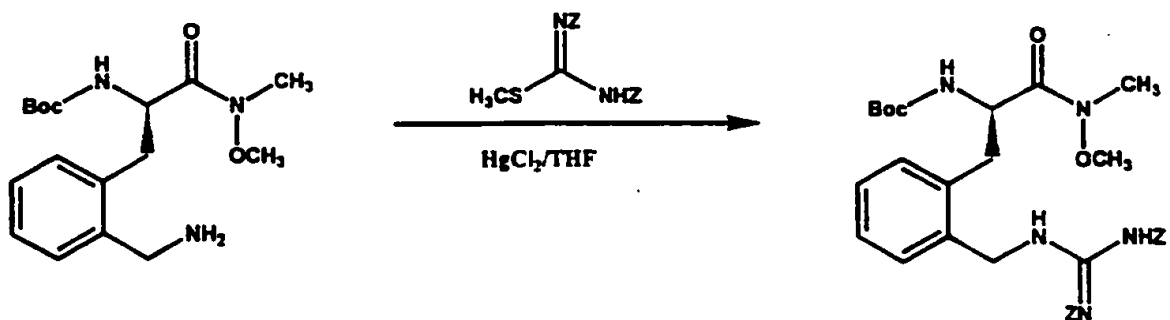


10 tert-Butyloxycarbonyl-para-aminomethyl-phenylalanine-N,O-dimethylamide (1.00 g, 3.1 mmol) was dissolved in dry THF (10 mL) under nitrogen with stirring. The solution was cooled, N,N'-bis-(benzyloxycarbonyl)-S-methyl-isothiourea (1.14 g, 3.2 mmol), and HgCl_2 (0.95 g, 3.5 mmol) added. The solution was concentrated under reduced pressure, the remaining residue was suspended in ethyl acetate (200 mL), and filtered through celite. The filtrate was concentrated under reduced pressure. Flash chromatography over silica gel (hexane/ethyl acetate gradient) afforded the purified compound.



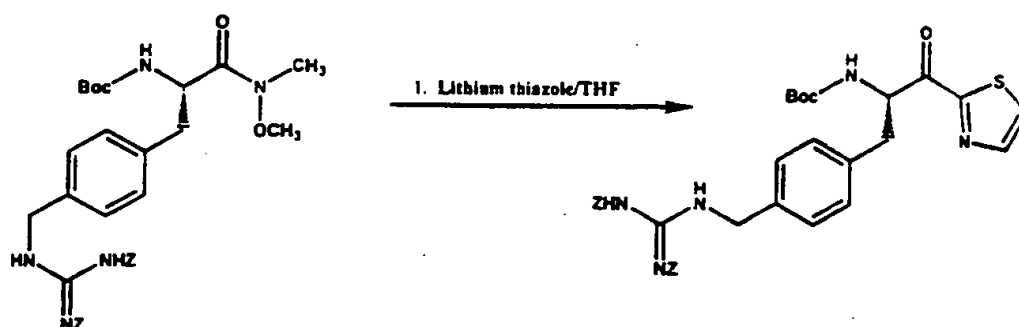
tert-Butyloxycarbonyl-meta-aminomethyl-phenylalanine-N,O-dimethylamide (1.00 g, 3.1 mmol) was dissolved in dry THF (10 mL) under nitrogen with stirring. The solution was cooled, N,N'-bis-(benzyloxycarbonyl)-S-methyl-isothiourea (1.14 g, 3.2 mmol), and HgCl₂ (0.95 g, 3.5 mmol) added. The solution was concentrated under reduced pressure, the remaining residue was suspended in ethyl acetate (200 mL), and filtered through celite. The filtrate was concentrated under reduced pressure.

10 Flash chromatography over silica gel (hexane/ethyl acetate gradient) afforded the purified compound.

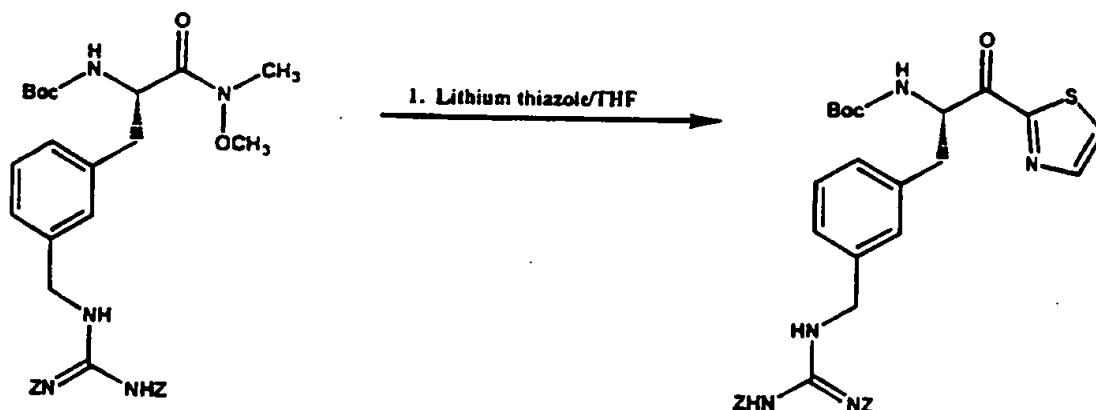


tert-Butyloxycarbonyl-ortho-aminomethyl-phenylalanine-N,O-dimethylamide (1.00 g, 3.1 mmol) was dissolved in dry THF (10

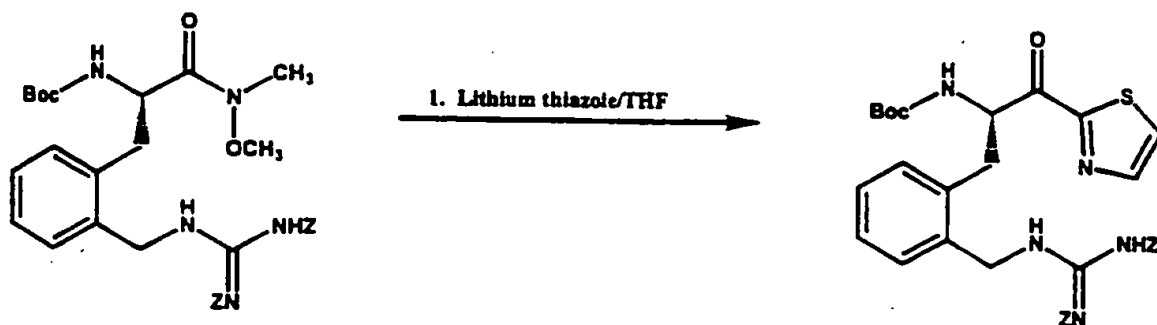
mL) under nitrogen with stirring. The solution was cooled, N,N'-bis-(benzyloxycarbonyl)-S-methyl-isothiourea (1.14 g, 3.2 mmol), and HgCl₂ (0.95 g, 3.5 mmol) added. The solution was concentrated under reduced pressure, the remaining residue was suspended in ethyl acetate (200 mL), and filtered through celite. The filtrate was concentrated under reduced pressure. Flash chromatography over silica gel (hexane/ethyl acetate gradient) afforded the purified compound.



- 10 To a solution of thiazole (1.28 g, 15.0 mmol) in anhydrous THF (30 mL) was added n-BuLi (1.6 M/hexane, 8.9 mL, 13.9 mmol) dropwise at -78° C, and the solution stirred. The protected amino acid (1.36 g, 3.3 mmol) in THF (15 mL) was then added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with MgSO₄, filtered, and concentrated under reduced pressure. The crude material was
- 20 purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.



To a solution of thiazole (1.28 g, 15.0 mmol) in anhydrous THF (30 mL) was added *n*-BuLi (1.6 M/hexane, 8.9 mL, 13.9 mmol) dropwise at -78°C , and the solution stirred. The protected amino acid (1.36 g, 3.3 mmol) in THF (15 mL) was then added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with MgSO_4 , filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.



PCL XL error

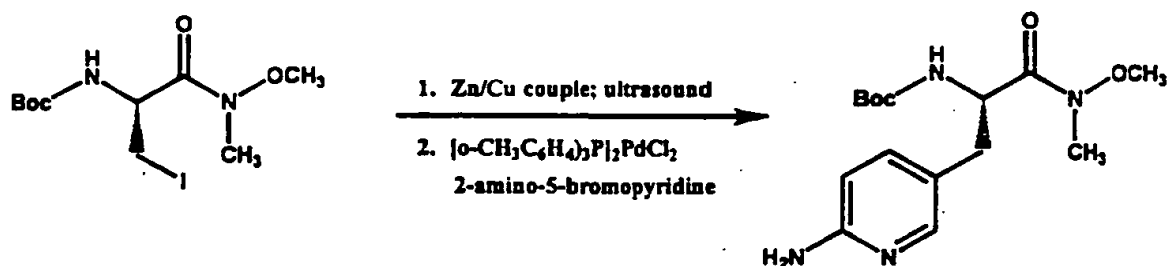
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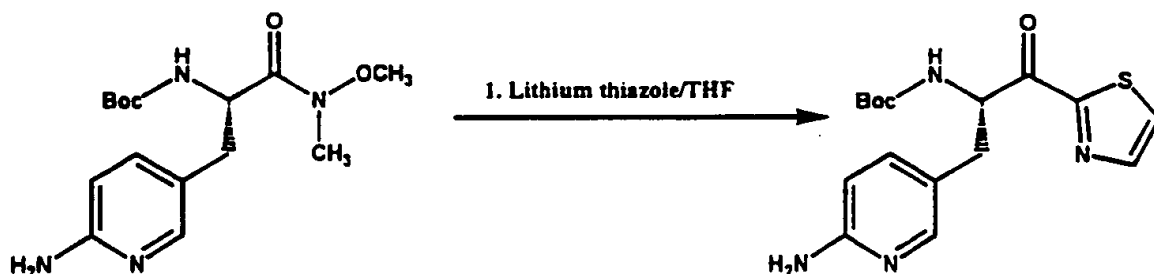
Position: 10137

To a solution of thiazole (1.28 g, 15.0 mmol) in anhydrous THF (30 mL) was added *n*-BuLi (1.6 M/hexane, 8.9 mL, 13.9 mmol) dropwise at -78° C, and the solution stirred. The protected amino acid (1.36 g, 3.3 mmol) in THF (15 mL) was then added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.

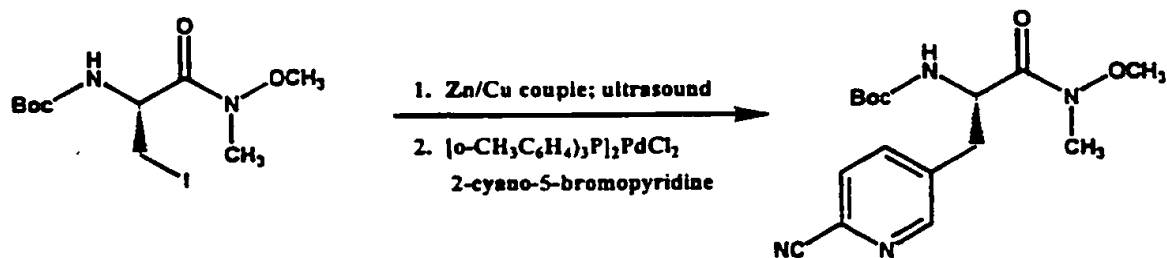


A solution of tert-butyloxycarbonyl-iodo-alanine-N,O-dimethylamide (2.68 g, 7.5 mmol) (J. Org. Chem. 1992, 57, 3397-3404) in dry benzene (30 mL), and dry N,N-dimethylacetamide (2.0 mL) was added to a dry nitrogen-purged round bottom flask charged with zinc-copper couple (0.90 g). The resulting mixture was sonicated under nitrogen until no starting material remained (as judged by TLC). Bis(tri-*o*-tolylphosphine)palladium dichloride (0.35 g, 0.40 mmol) was added followed by 2-iodobenzonitrile (1.72 g, 7.5 mmol). The resulting mixture was stirred under a nitrogen atmosphere with heating, allowed to cool, ethyl acetate (100 mL) was added, and the mixture filtered into a separatory funnel. Sequential

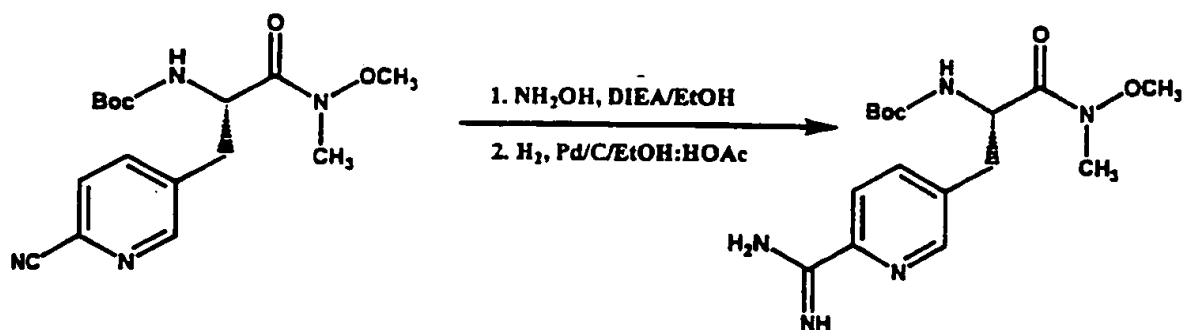
washing with aqueous HCl (50 mL; 0.1N), distilled H₂O (3 x 50 mL), drying over Na₂SO₄, filtration, and concentration under reduced pressure yielded the crude product. Flash chromatography over silica gel (light petroleum/ethyl acetate gradient) afforded the purified compound.



To a solution of thiazole (1.28 g, 15.0 mmol) in anhydrous THF (30 mL) was added *n*-BuLi (1.6 M/hexane, 8.9 mL, 13.9 mmol) dropwise at -78° C, and the solution stirred. The amino acid-N,O-dimethylamide (1.07 g, 3.3 mmol) in anhydrous THF (15 mL) was then added dropwise and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with MgSO₄, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.

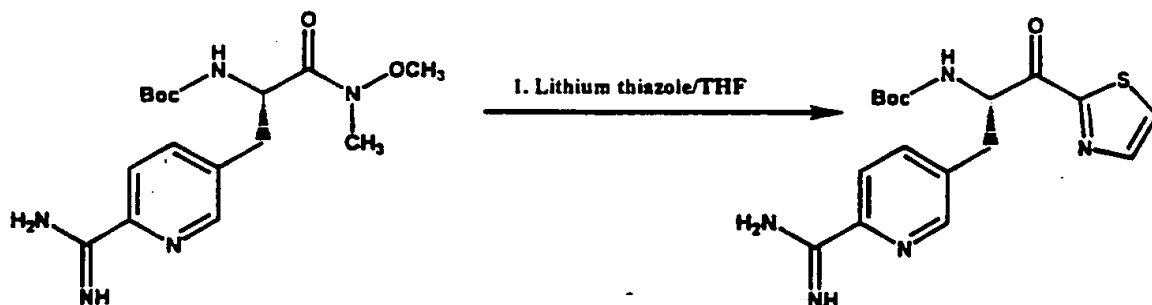


A solution of tert-butyloxycarbonyl-iodo-alanine-N,O-dimethylamide (2.68 g, 7.5 mmol) (J. Org. Chem. 1992, 57, 3397-3404) in dry benzene (30 mL), and dry N,N-dimethylacetamide (2.0 mL) was added to a dry nitrogen-purged round bottom flask charged with zinc-copper couple (0.90 g). The resulting mixture was sonicated under nitrogen until no starting material remained (as judged by TLC). Bis(tri-o-tolylphosphine)palladium dichloride (0.35 g, 0.40 mmol) was added followed by 2-iodobenzonitrile (1.72 g, 7.5 mmol). The resulting mixture was stirred under a nitrogen atmosphere with heating, allowed to cool, ethyl acetate (100 mL) was added, and the mixture filtered into a separatory funnel. Sequential washing with aqueous HCl (50 mL; 0.1N), distilled H₂O (3 x 50 mL), drying over Na₂SO₄, filtration, and concentration under reduced pressure yielded the crude product. Flash chromatography over silica gel (light petroleum/ethyl acetate gradient) afforded the purified compound.



To a solution of tert-butyloxycarbonyl-(4-cyano)-3-pyridyl-L-alanine-N,O-dimethylamide (1.34 g, 4.0 mmol) in dry ethanol (20 mL) was added N,O-hydroxylamine hydrochloride (0.416 g, 6.0 mmol), and diisopropylethylamine (1.02 mL, 6.0 mmol). The mixture was refluxed and then cooled. The precipitate was filtered, washed with cold ethanol,

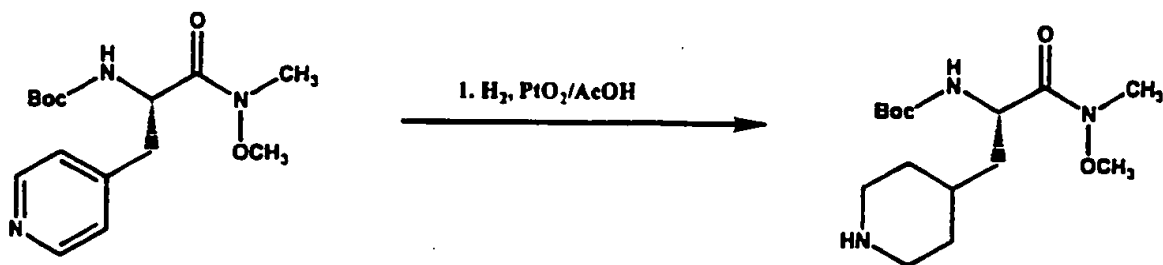
diisopropylether, dried with MgSO_4 , concentrated under reduced pressure, and used directly in the next step. The semi-solid was suspended in a mixture of acetic acid (20 mL), and dry ethanol (40 mL) with warming. Subsequently, Pd/C catalyst (0.30 g, 10% Pd) was added, and hydrogen was bubbled through the mixture with warming. The hydrogenation was continued until no starting material could be detected as judged by TLC. The catalyst was removed by filtration, and the solution was concentrated under reduced pressure (50 mL), HCl (50 mL, 1 N) was added, and the mixture was concentrated once again to 50 mL. The solution was chilled overnight yielding the title compound.



To a solution of thiazole (1.28 g, 15.0 mmol) in anhydrous THF (30 mL) was added *n*-BuLi (1.6 M/hexane, 8.9 mL, 13.9 mmol) dropwise at -78°C , and the solution stirred. The amino acid-N,O-dimethylamide (1.16 g, 3.3 mmol) in anhydrous THF (15 mL) was then added dropwise, and the resulting mixture stirred.

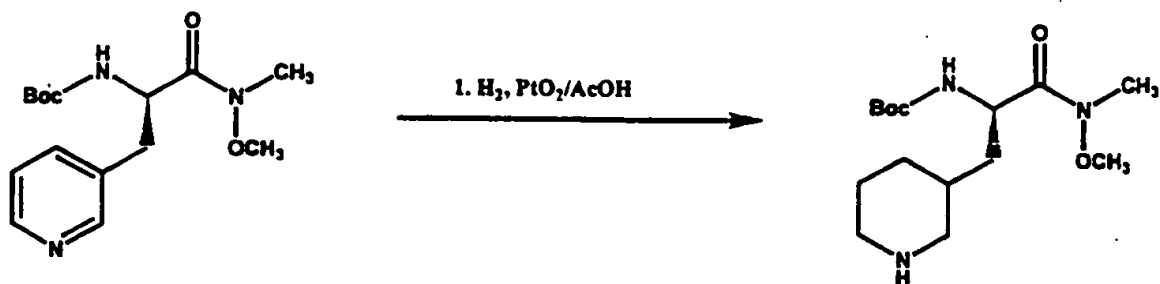
The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with MgSO_4 , filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and

concentrated under reduced pressure.



tert-Butyloxycarbonyl-3-(4-pyridyl)alanine-N,O-dimethylamide (4.50 g, 14.4 mmol) was dissolved in acetic acid (100 mL), and PtO₂ (100 mg) added. The solution was shaken under H₂ until gas uptake ceased. The solution was filtered through celite, and concentrated under reduced pressure yielding *tert*-butyloxycarbonyl-3-(4-piperidyl)alanine-N,O-dimethylamide.

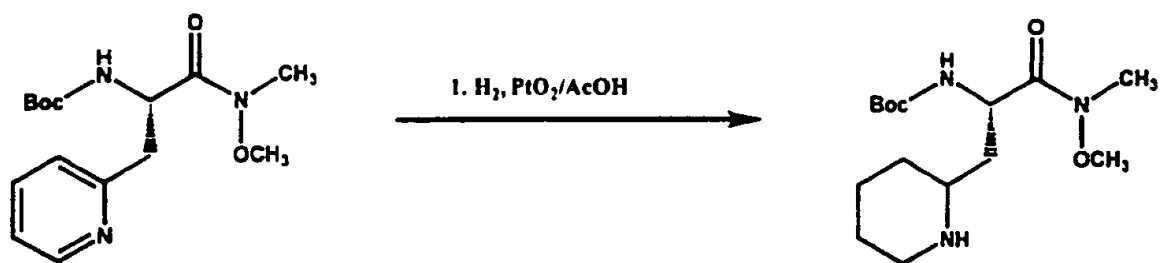
- 10 The residue was dissolved in ethyl acetate (250 mL), washed with 1 N NaOH (2 x 50 mL), brine (2 x 50 mL), dried with MgSO₄, filtered, and concentrated under reduced pressure to yield the title compound.



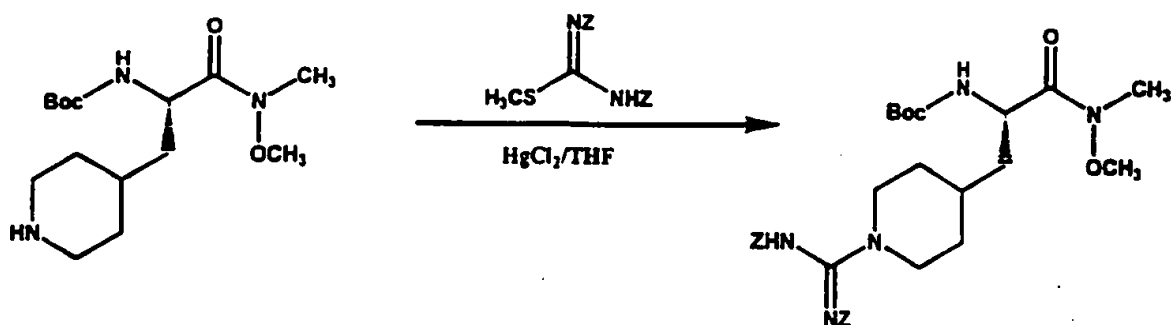
tert-Butyloxycarbonyl-3-(3-pyridyl)alanine-N,O-dimethylamide (4.50 g, 14.4 mmol) was dissolved in acetic acid (100 mL), and PtO₂ (100 mg) added. The solution was shaken under H₂ until gas uptake ceased. The solution was filtered through celite,

and concentrated under reduced pressure yielding tert-butylloxycarbonyl-3-(3-piperidyl)alanine-N,O-dimethylamide.

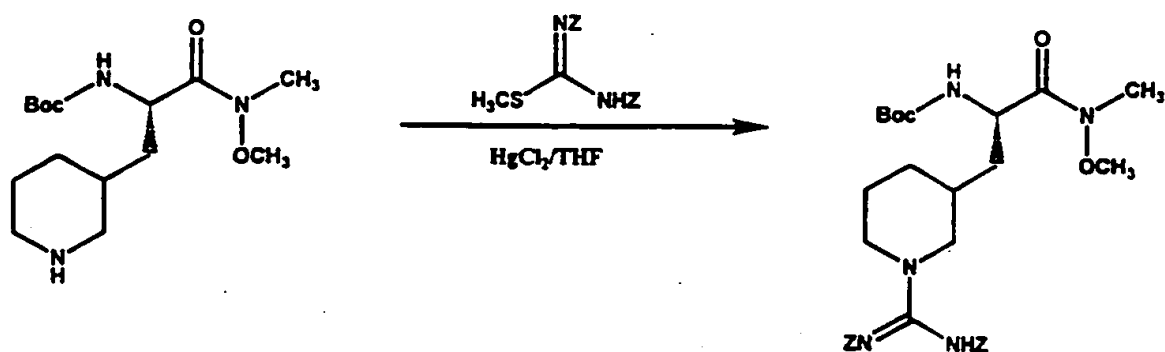
The residue was dissolved in ethyl acetate (250 mL), washed with 1 N NaOH (2 x 50 mL), brine (2 x 50 mL), dried with MgSO_4 , filtered, and concentrated under reduced pressure to yield the title compound.



tert-Butylloxycarbonyl-3-(2-pyridyl)alanine-N,O-dimethylamide
 10 (4.50 g, 14.4 mmol) was dissolved in acetic acid (100 mL), and
 PtO₂ (100 mg) added. The solution was shaken under H₂ until
 gas uptake ceased. The solution was filtered through celite,
 and concentrated under reduced pressure yielding tert-
 butylloxycarbonyl-3-(2-piperidyl)alanine-N,O-dimethylamide.
 The residue was dissolved in ethyl acetate (250 mL), washed
 with 1 N NaOH (2 x 50 mL), brine (2 x 50 mL), dried with MgSO_4 ,
 filtered, and concentrated under reduced pressure to yield the
 title compound.

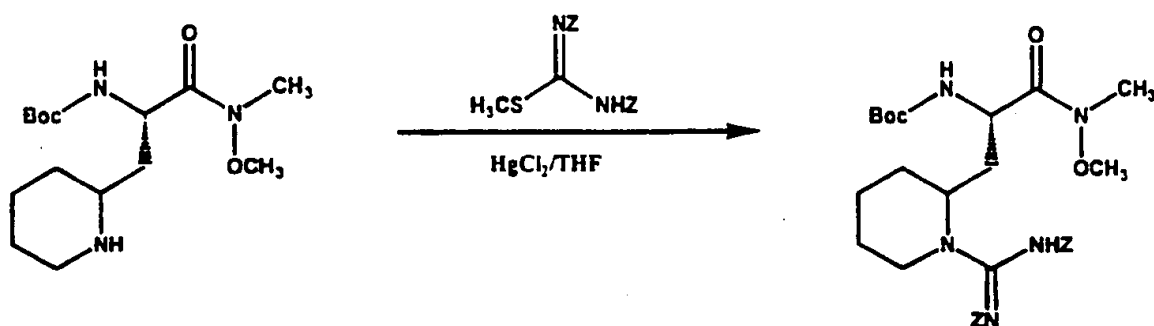


tert-Butyloxycarbonyl-3-(4-piperidyl)alanine-*N*,*O*-dimethylamide (1.00 g, 3.2 mmol) was dissolved in dry THF (10 mL) under nitrogen with stirring. The solution was cooled, *N*,*N'*-bis-(benzyloxycarbonyl)-*S*-methyl-isothiourea (1.14 g, 3.2 mmol), and HgCl_2 (0.95 g, 3.5 mmol) added. The solution was concentrated under reduced pressure, the remaining residue was suspended in ethyl acetate (200 mL), and filtered through celite. The filtrate was concentrated under reduced pressure. Flash chromatography over silica gel (hexane/ethyl acetate gradient) afforded the title compound.

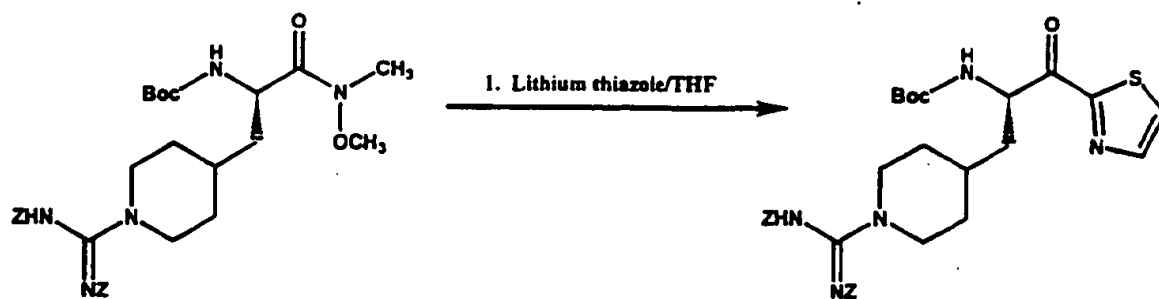


tert-Butyloxycarbonyl-3-(3-piperidyl)alanine-*N*,*O*-dimethylamide (1.00 g, 3.2 mmol) was dissolved in dry THF (10 mL) under nitrogen with stirring. The solution was cooled, *N*,*N'*-bis-

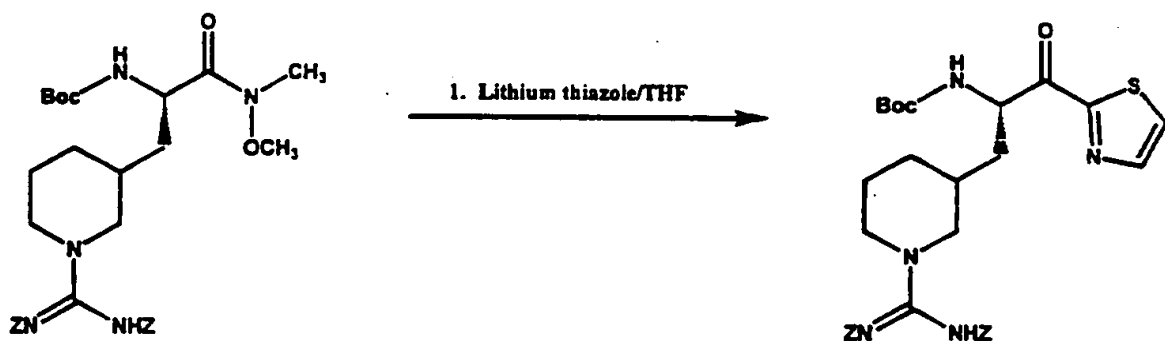
(benzyloxycarbonyl)-S-methyl-isothioureia (1.14 g, 3.2 mmol), and HgCl_2 (0.95 g, 3.5 mmol) added. The solution was concentrated under reduced pressure, the remaining residue was suspended in ethyl acetate (200 mL), and filtered through celite. The filtrate was concentrated under reduced pressure. Flash chromatography over silica gel (hexane/ethyl acetate gradient) afforded the title compound.



- 10 tert-Butyloxycarbonyl-3-(2-piperidyl)alanine-N,O-dimethylamide (1.00 g, 3.2 mmol) was dissolved in dry THF (10 mL) under nitrogen with stirring. The solution was cooled, N,N'-bis-(benzyloxycarbonyl)-S-methyl-isothioureia (1.14 g, 3.2 mmol), and HgCl_2 (0.95 g, 3.5 mmol) added. The solution was concentrated under reduced pressure, the remaining residue was suspended in ethyl acetate (200 mL), and filtered through celite. The filtrate was concentrated under reduced pressure. Flash chromatography over silica gel (hexane/ethyl acetate gradient) afforded the title compound.

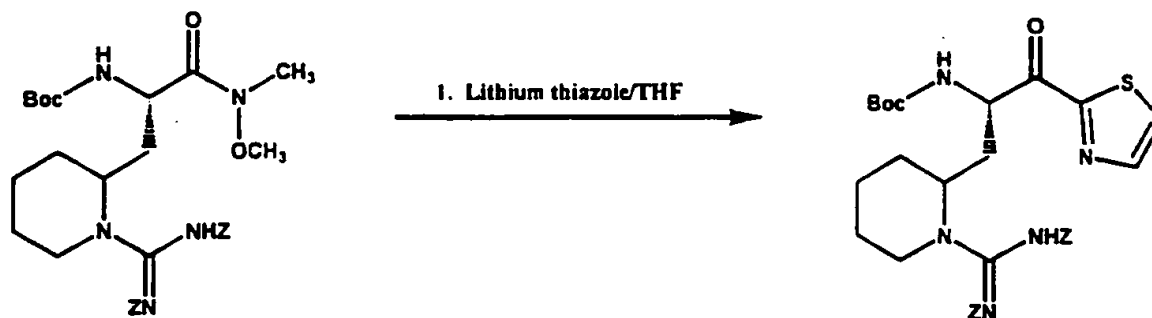


To a solution of thiazole in anhydrous THF (1.23 g, 14.4 mmol) was added *n*-BuLi (1.6 M/hexane, 8.4 mL, 13.4 mmol) dropwise at -78°C and the solution stirred. The guanidylated 4-piperidylalanine derivative (2.00 g, 3.2 mmol) in anhydrous THF (15 mL) was added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with MgSO_4 , filtered, and concentrated under reduced pressure.

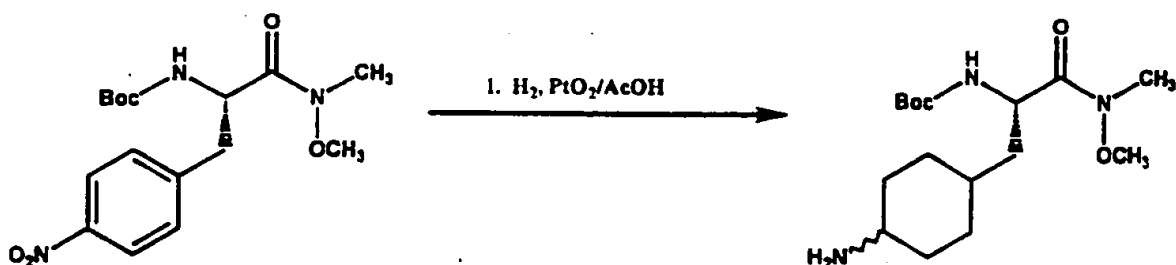


To a solution of thiazole in anhydrous THF (1.23 g, 14.4 mmol) was added *n*-BuLi (1.6 M/hexane, 8.4 mL, 13.4 mmol) dropwise at -78°C with stirring. The mixture was stirred at -78°C for 1 h. The guanidylated 3-piperidylalanine derivative (2.00 g,

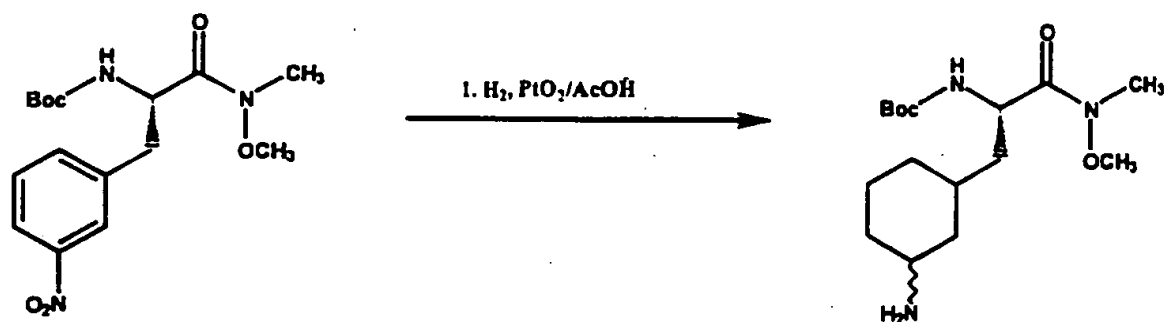
3.2 mmol) in THF (15 mL) was added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with MgSO_4 , filtered, and concentrated under reduced pressure.



10 To a solution of thiazole in anhydrous THF (1.23 g, 14.4 mmol) was added $n\text{-BuLi}$ (1.6 M/hexane, 8.4 mL, 13.4 mmol) dropwise at -78°C with stirring. The mixture was stirred at -78°C for 1 h. The guanidylated 2-piperidylalanine derivative (2.00 g, 3.2 mmol) in THF (15 mL) was added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with MgSO_4 , filtered, and concentrated under reduced pressure.

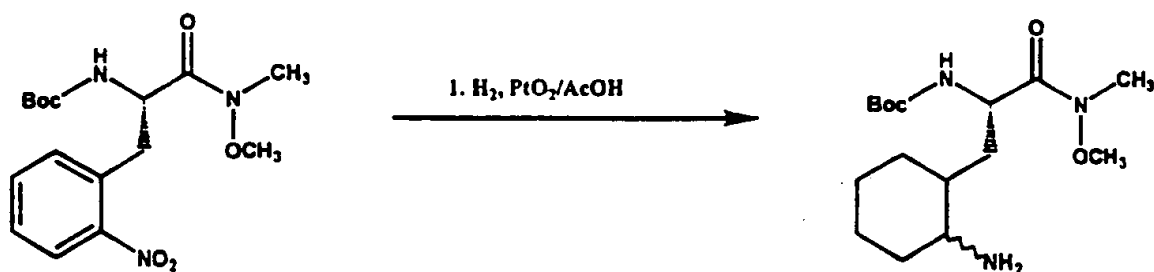


tert-Butyloxycarbonyl-para-nitro-phenylalanine-N,O-dimethylamide (13.88 g, 39.3 mmol) was dissolved in acetic acid (100 mL), and PtO₂ (100 mg) added. The solution was shaken under H₂ until gas uptake ceased. The solution was filtered through celite, concentrated under reduced pressure, taken up in H₂O (150 mL), and lyophilized. The semi-solid was dissolved in ethyl acetate (350 mL), washed with 1 N NaOH (3 x 50 mL), and brine (3 x 50 mL). The solution was dried with
 10 MgSO₄, filtered, and concentrated under reduced pressure yielding the title compound.

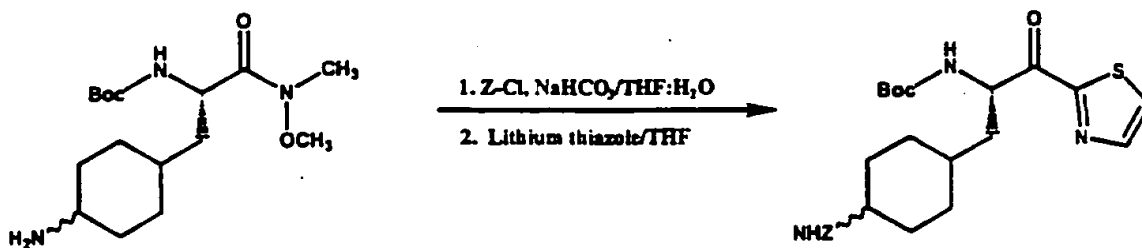


tert-Butyloxycarbonyl-meta-nitro-phenylalanine-N,O-dimethylamide (13.88 g, 39.3 mmol) was dissolved in acetic acid (100 mL), and PtO₂ (100 mg) added. The solution was shaken under H₂ until gas uptake ceased. The solution was filtered through celite, concentrated under reduced pressure, taken up in H₂O (150 mL), and lyophilized. The semi-solid was

dissolved in ethyl acetate (350 mL), washed with 1 N NaOH (3 x 50 mL), and brine (3 x 50 mL). The solution was dried with MgSO_4 , filtered, and concentrated under reduced pressure yielding the title compound.



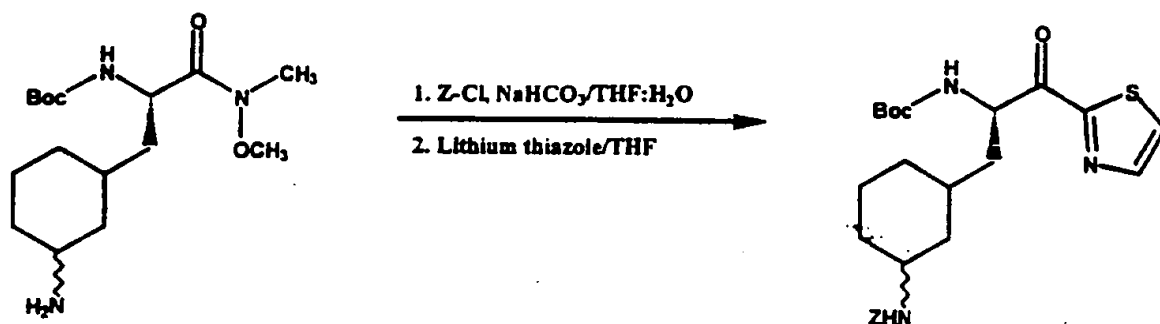
tert-Butyloxycarbonyl-ortho-nitro-phenylalanine-N,O-dimethylamide (13.88 g, 39.3 mmol) was dissolved in acetic acid (100 mL), and PtO_2 (100 mg) added. The solution was shaken under H_2 until gas uptake ceased. The solution was filtered through celite, concentrated under reduced pressure, taken up in H_2O (150 mL), and lyophilized. The semi-solid was dissolved in ethyl acetate (350 mL), washed with 1 N NaOH (3 x 50 mL), and brine (3 x 50 mL). The solution was dried with MgSO_4 , filtered, and concentrated under reduced pressure yielding the title compound.



1. tert-Butyloxycarbonyl-3-(cis/trans-4-aminocyclohexyl)alanine-N,O-dimethylamide (1.00 g, 3.0 mmol) was dissolved in saturated aqueous sodium bicarbonate, and THF

[60 mL, (1:1)] with stirring. The solution was cooled and a solution of benzyl chloroformate (0.43 mL, 3.0 mmol) in THF (10 mL) was added dropwise. Excess solid sodium bicarbonate was added, the THF was removed under reduced pressure, and the remaining aqueous phase was poured into ethyl acetate (250 mL), and mixed thoroughly. The aqueous phase was discarded and the remaining solution was washed with saturated aqueous sodium bicarbonate (2 x 50 mL), 4 N aqueous sodium bisulfate (2 x 50 mL), and brine (2 x 50 mL). The solution was dried
10 with MgSO_4 , filtered, and concentrated under reduced pressure. The semi-solid was chromatographed on silica gel (ethyl acetate/ hexane).

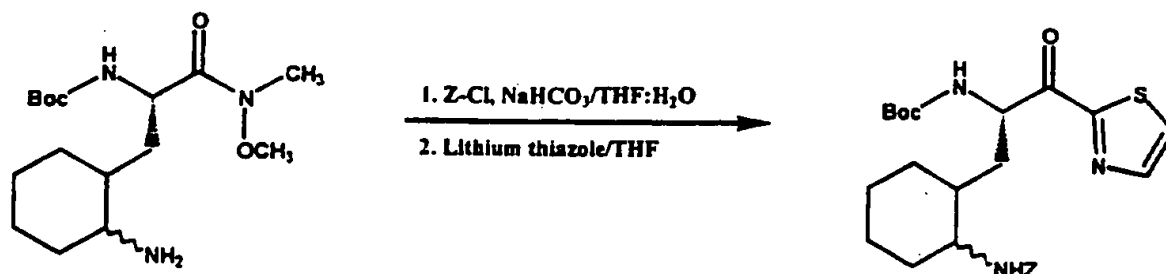
2. To a solution of thiazole (1.16 g, 13.7 mmol) in anhydrous THF was added *n*-BuLi (1.6 M/hexane, 8.0 mL, 12.8 mmol) dropwise at -78°C and the solution stirred. The above protected amino acid amide (1.41 g, 3.0 mmol) in THF (15 mL) was added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium
20 chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with MgSO_4 , filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.



1. tert-Butyloxycarbonyl-3-(*cis/trans*-3-aminocyclohexyl)alanine-N,O-dimethylamide (1.00 g, 3.0 mmol) was dissolved in saturated aqueous sodium bicarbonate, and THF [60 mL, (1:1)] with stirring. The solution was cooled and a solution of benzyl chloroformate (0.43 mL, 3.0 mmol) in THF (10 mL) was added dropwise. Excess solid sodium bicarbonate was added, the THF was removed under reduced pressure, and the remaining aqueous phase was poured into ethyl acetate (250 mL), and mixed thoroughly. The aqueous phase was discarded and the remaining solution was washed with saturated aqueous sodium bicarbonate (2 x 50 mL), 4 N aqueous sodium bisulfate (2 x 50 mL), and brine (2 x 50 mL). The solution was dried with MgSO₄, filtered, and concentrated under reduced pressure. The semi-solid was chromatographed on silica gel (ethyl acetate/ hexane).

2. To a solution of thiazole (1.16 g, 13.7 mmol) in anhydrous THF was added *n*-BuLi (1.6 M/hexane, 8.0 mL, 12.8 mmol) dropwise at -78° C and the solution stirred. The above protected amino acid amide (1.41 g, 3.0 mmol) in THF (15 mL) was added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous

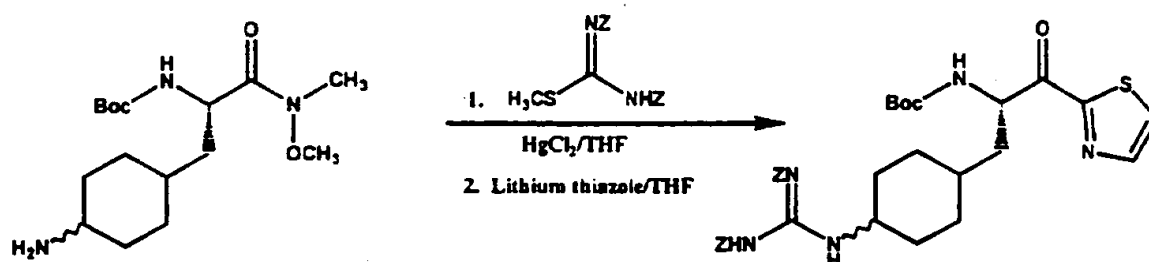
ammonium chloride (2 x 50 mL), brine (50 mL), dried with MgSO_4 , filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.



1. *tert*-Butyloxycarbonyl-3-(*cis/trans*-2-aminocyclohexyl)alanine-*N,O*-dimethylamide (1.00 g, 3.0 mmol) was dissolved in saturated aqueous sodium bicarbonate, and THF [60 mL, (1:1)] with stirring. The solution was cooled and a solution of benzyl chloroformate (0.43 mL, 3.0 mmol) in THF (10 mL) was added dropwise. Excess solid sodium bicarbonate was added, the THF was removed under reduced pressure, and the remaining aqueous phase was poured into ethyl acetate (250 mL), and mixed thoroughly. The aqueous phase was discarded and the remaining solution was washed with saturated aqueous sodium bicarbonate (2 x 50 mL), 4 N aqueous sodium bisulfate (2 x 50 mL), and brine (2 x 50 mL). The solution was dried with MgSO_4 , filtered, and concentrated under reduced pressure. The semi-solid was chromatographed on silica gel (ethyl acetate/ hexane).

2. To a solution of thiazole (1.16 g, 13.7 mmol) in anhydrous THF was added *n*-BuLi (1.6 M/hexane, 8.0 mL, 12.8 mmol) dropwise at -78°C and the solution stirred. The above protected amino acid amide (1.41 g, 3.0 mmol) in THF (15 mL)

was added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with MgSO_4 , filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.



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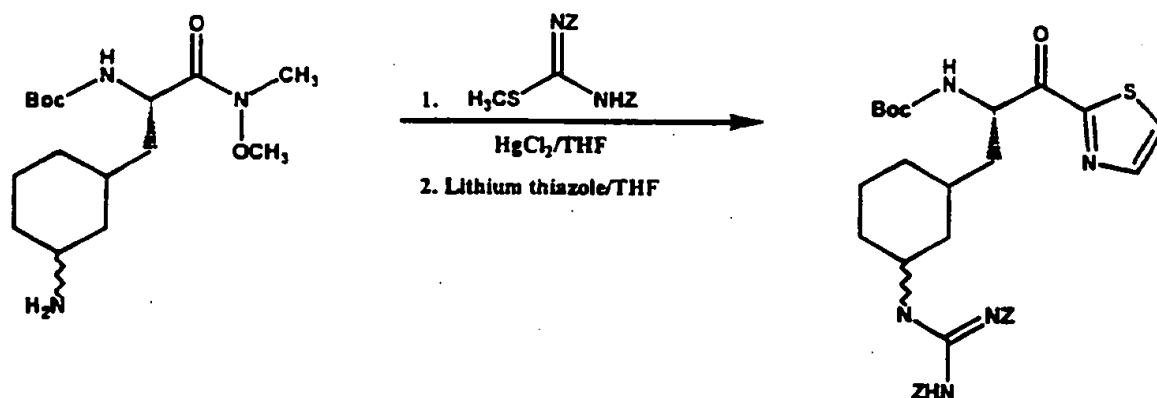
1. *tert*-Butyloxycarbonyl-3-(*cis/trans*-4-aminocyclohexyl)alanine-*N,O*-dimethylamide (2.0 g, 6.1 mmol) was dissolved in dry THF (20 mL) under nitrogen with stirring. The solution was cooled to 0° C, *N,N'*-bis-(benzyloxycarbonyl)-*S*-methyl-isothiourea (2.18 g, 6.1 mmol), and HgCl_2 (1.81 g, 6.7 mmol) added. The solution was concentrated under reduced pressure, the remaining residue was suspended in ethyl acetate (300 mL), and filtered through celite. The filtrate was concentrated under reduced pressure. Flash chromatography over silica gel (hexane/ethyl acetate gradient) afforded the purified product.

20

2. To a solution of thiazole (2.32 g, 27.3 mmol) in anhydrous THF was added *n*-BuLi (1.6 M/hexane, 15.9 mL, 25.4 mmol) dropwise at -78° C and the solution stirred. The above

guanidylated amino acid (3.88 g, 6.1 mmol) in THF (15 mL) was added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with MgSO_4 , filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.

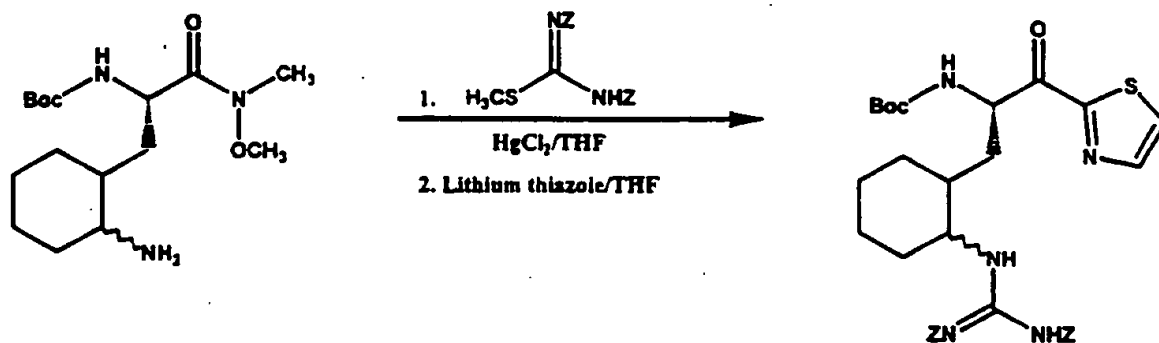
10



1. *tert*-Butyloxycarbonyl-3-(*cis/trans*-3-aminocyclohexyl)alanine-*N,O*-dimethylamide (2.0 g, 6.1 mmol) was dissolved in dry THF (20 mL) under nitrogen with stirring. The solution was cooled to 0° C, *N,N'*-bis-(benzyloxycarbonyl)-*S*-methyl-isothiouraea (2.18 g, 6.1 mmol), and HgCl_2 (1.81 g, 6.7 mmol) added. The solution was concentrated under reduced pressure, the remaining residue was suspended in ethyl acetate (300 mL), and filtered through celite. The filtrate was concentrated under reduced pressure. Flash chromatography over silica gel (hexane/ethyl acetate gradient) afforded the purified product.

20

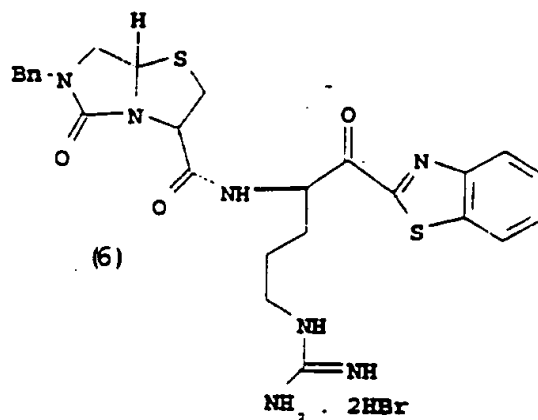
2. To a solution of thiazole (2.32 g, 27.3 mmol) in anhydrous THF was added *n*-BuLi (1.6 M/hexane, 15.9 mL, 25.4 mmol) dropwise at -78° C and the solution stirred. The above guanidylated amino acid (3.88 g, 6.1 mmol) in THF (15 mL) was added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with MgSO₄, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.



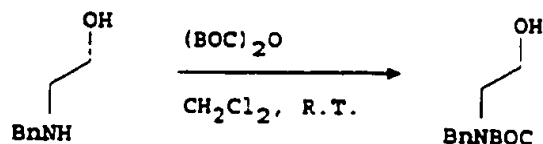
1. *tert*-Butyloxycarbonyl-3-(*cis/trans*-2-aminocyclohexyl)alanine-*N,O*-dimethylamide (2.0 g, 6.1 mmol) was dissolved in dry THF (20 mL) under nitrogen with stirring. The solution was cooled to 0° C, *N,N'*-bis-(benzyloxycarbonyl)-*S*-methyl-isothiourea (2.18 g, 6.1 mmol), and HgCl_2 (1.81 g, 6.7 mmol) added. The solution was concentrated under reduced pressure, the remaining residue was suspended in ethyl acetate (300 mL), and filtered through celite. The filtrate was

concentrated under reduced pressure. Flash chromatography over silica gel (hexane/ethyl acetate gradient) afforded the purified product.

2. To a solution of thiazole (2.32 g, 27.3 mmol) in anhydrous THF was added *n*-BuLi (1.6 M/hexane, 15.9 mL, 25.4 mmol) dropwise at -78°C and the solution stirred. The above guanidylated amino acid (3.88 g, 6.1 mmol) in THF (15 mL) was added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with MgSO_4 , filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.

EXAMPLE 2**SYNTHESIS OF COMPOUND # 6**

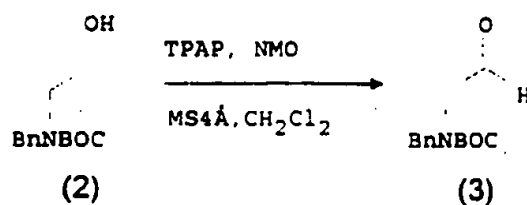
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STEP 1

(1)

(2)

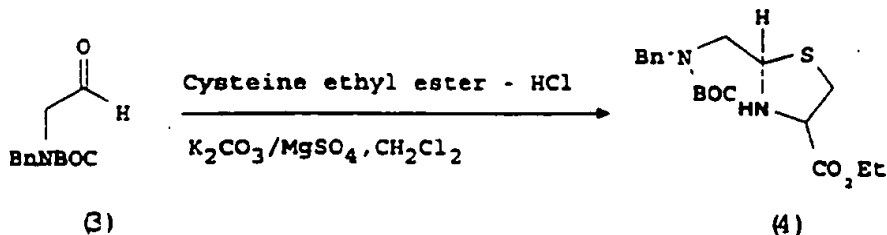
On equivalent of di-tert-butyl dicarbonate (5.56 g; 25.0 mmols) was added to a solution of N-benzylethanolamine (1) (3.92 g; 26.0 mmols) in CH_2Cl_2 (75 ml). The solution was stirred at room temperature overnight. Evaporation of the solvent gave the N-Boc protected amine (2) (6.61 g; 100%).

STEP 2

10

Tetrapropylammonium perruthenate (TPAP) (67 mg; 4.23 mmols) was added to a well stirred mixture of the alcohol (2) (608 mg; 4.23 mmols) and powdered 4Å molecular sieves (1.5 g) in dichloromethane (10 ml). After being stirred for 20 minutes, the mixture was filtered through celite™. Evaporation of the solvent gave a black oil which was then purified on silica gel (ethyl acetate (EtOAc) 30%; Hexanes 70%) to give the aldehyde (3) (410 mg; 68%) as a colorless oil.

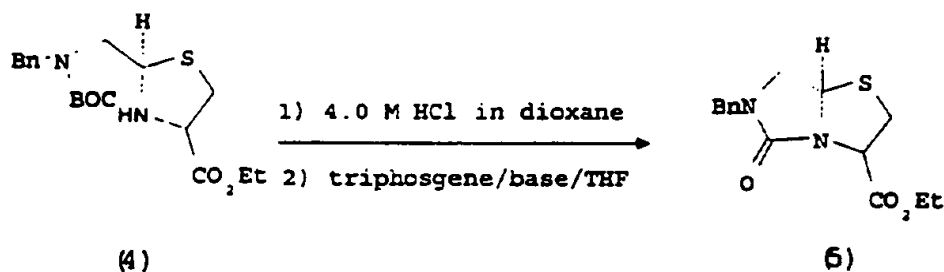
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STEP 3

A mixture of the aldehyde (3) (387 mg; 1.82 mmols), cysteine ethyl ester hydrochloride (370 mg; 1.99 mmols), potassium

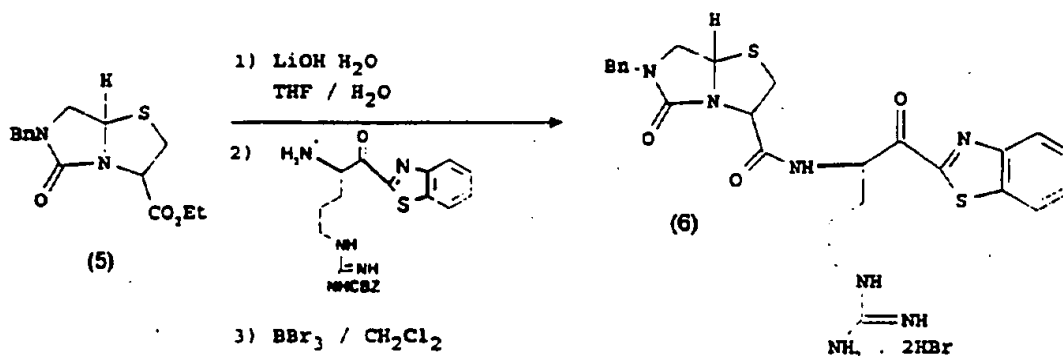
carbonate (1.2 g) and magnesium sulphate (1.2 g) in dichloromethane (10 ml) was stirred at room temperature for 18 hours. The resulting mixture was then transferred into an aqueous saturated solution of saturated NaHCO_3 (30 ml) and extracted with dichloromethane (3 x 30 ml). The combined organic layers were dried (MgSO_4) and the solvent evaporated to give an oil which was purified on silica gel (EtOAc 20%, Hexanes 80%) to give the thioamine (4) 439 mg; 70%) as a mixture of diastereoisomers.

10

STEP 4

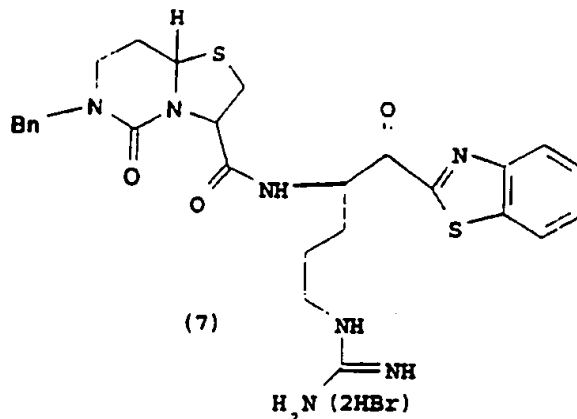
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4.0 M HCl in dioxane (15 ml; 60 mmols) is added to a mixture of the thioamine (4) (367 mg; 1.07 mmols) and ethylmethyl sulfide (1 ml). The resulting solution is stirred 3 hours. Evaporation of the solvent gives the crude deprotected amine as a mixture of isomers. The crude deprotected amine is solubilized in THF (15 ml) and diisopropylethylamine (0.7 ml). Triphosgene (400 mg; 1.34 mmols) is added to the solution and the resulting mixture is stirred at room temperature overnight. The mixture is then transferred into aqueous saturated NaHCO_3 (30 ml) and extracted with dichloromethane (3 x 30 ml). The combined organic layers are dried (MgSO_4) and evaporation of the solvents gives an oil that is purified on silica gel to give the compound (5).

STEP 5

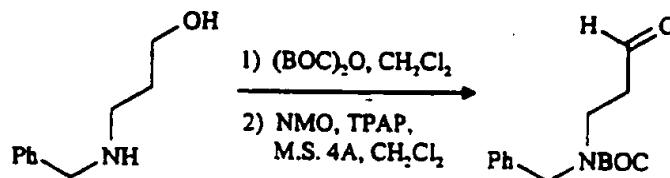
The isolated urea (5a) is hydrolyzed with one equivalent of LiOH•H₂O in a 1:1 mixture of THF and H₂O. The mixture is stirred at room temperature for 1 hour and the resulting solution is poured into 10% citric acid and extracted with dichloromethane to yield the crude carboxylic acid. The crude carboxylic acid is coupled with benzothiazole keto arginine in DMF using BOP as the coupling reagent in the presence of diisopropylethylamine. Extraction with EtOAc gives a solid that is purified on silica gel to give the protected amide. The CBZ protecting group is removed with BBr₃ in dichloromethane at room temperature finally gives the bicyclic benzothiazole keto arginine inhibitors (6).

EXAMPLE 3 Synthesis of compound 7



The urea of formula (7) is produced according to the same method as for the bicyclic benzothiazole keto arginine inhibitors (6) with the difference that the N-benzylethanolamine (1) is substituted by N-Benzyl-3-amino-propanol.

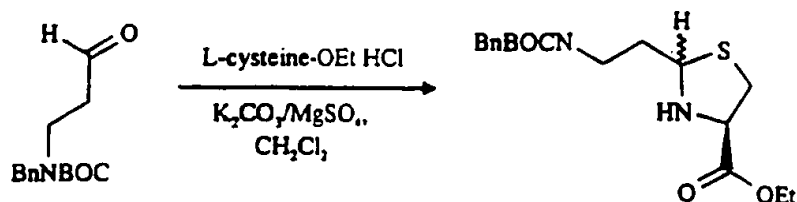
10 **EXAMPLE 4** Synthesis of compounds 13a and 13b



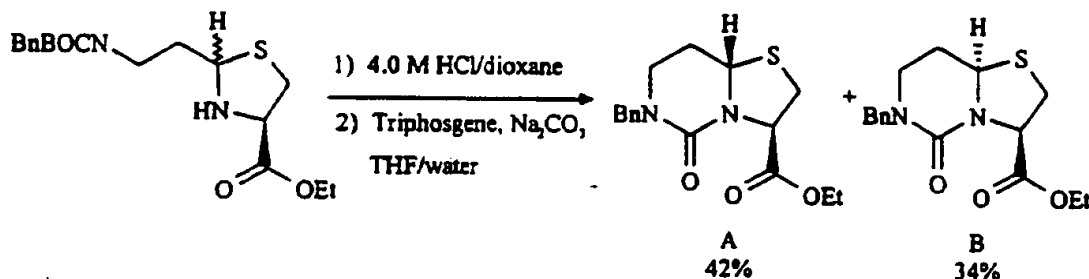
A solution of the amine (5.32 g, 0.032 mol) in CH_2Cl_2 (100 ml) was treated with $(\text{BOC})_2\text{O}$ (7.10 g, 0.038 mol). The solution was stirred at room temperature for 24 hours to afford after evaporation of the solvent the crude protected amine (8.25 g, 97%) which was used in the next step without further

20 purification. To the amine (5.18 g, 0.0195 mol) in CH_2Cl_2 (100 ml) was added powdered 4Å M.S. (12.6 g) and treated with NMO (4.21 g, 0.0359 mol) and TPAP (341 mg, 0.972 mmol). The mixture was stirred at room temperature for 30 minutes, then

filtered on a path of celite. Purification on silica gel (20% EtOAc/80% hex) afforded the aldehyde (2.76 g, 54%).

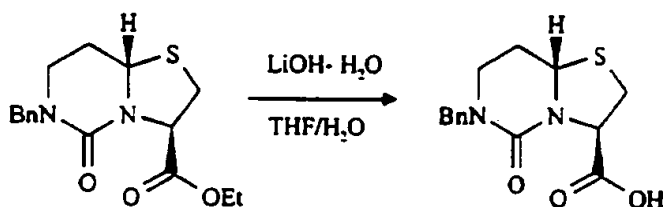


A mixture of the aldehyde (2.76 g, 0.0105 mols), L-cysteine ethyl ester • HCl (2.91 g, 15.7 mmols), potassium carbonate (9 g) and magnesium sulphate (9 g) in CH₂Cl₂ (75 ml) were stirred at room temperature for 17 hours. The mixture was poured into NaHCO_{3(s)} (200 ml) and extracted with CH₂Cl₂ (3x200 ml). The combined organic phases were dried (MgSO₄). Purification of the oil on silica gel (20% EtOAc/80% hex) afforded the thioaminal (3.54 g, 86%).



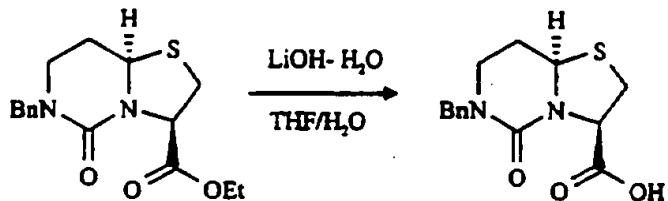
The protected amine (1.87 g, 0.0047 mol) dissolved in EtSMe (4 ml) was treated with 4.0 M HCl in dioxane (50 mL) and stirred for 75 minutes. The mixture was poured into a saturated solution of NaHCO₃ (200 ml) and an additional 20 g of NaHCO₃ was added. The aqueous mixture was extracted with EtOAc (3x200 ml) and the combined organic phases were washed (brine), dried (Na₂SO₄). Evaporation of the volatiles left the crude deprotected amine (1.35 g, 97%). The crude amine (1.23 g, 4.17 mmols) dissolved in THF (15 ml) and treated successively with a solution of Na₂CO₃ (885 mg) in water (15

ml) followed by a solution of triphosgene (408 mg, 1.37 mmols). The mixture was stirred at room temperature for 19 hours, then poured into water (60 ml) and extracted with CH_2Cl_2 (4x60 ml). The combined organic phases were washed with HCl 5% (200 ml), NaHCO_3 (200 ml), and dried (MgSO_4). Purification on silica gel afforded the urea A (568 mg, 42%) and the urea B (470 mg, 34%). The stereochemistry at the angular position is arbitrarily assigned.



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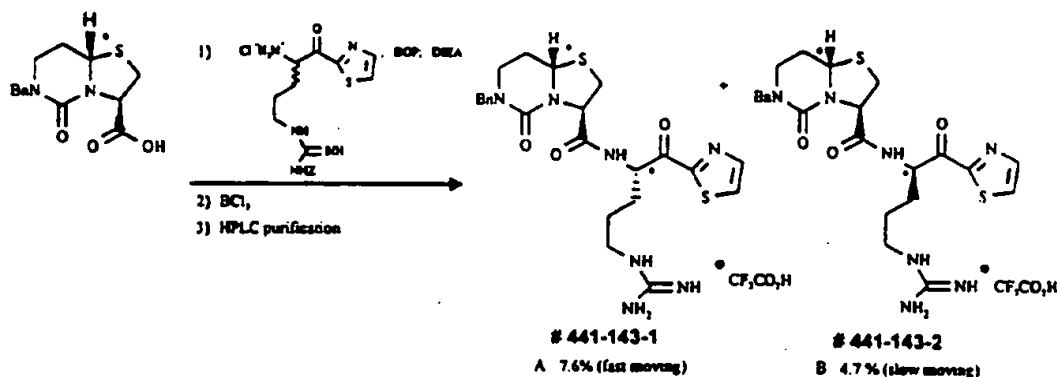
A solution of the ester (517 mg, 1.61 mmols) in THF (10 ml) was treated with $\text{LiOH} \cdot \text{H}_2\text{O}$ (74 mg, 1.8 mmols) in water (10 ml). The solution was stirred at room temperature for 60 minutes then poured into 5% HCl (50 ml) and extracted with CH_2Cl_2 (4x70 ml) and dried (MgSO_4). Evaporation of the solvent left the crude carboxylic acid (418 mg, 89%).



20

A solution of the ester (432 mg, 1.35 mmols) in THF (10 ml) was treated with $\text{LiOH} \cdot \text{H}_2\text{O}$ (161.6 mg, 3.85 mmols) in H_2O (10 ml). The mixture was stirred at room temperature overnight. The mixture was poured into HCl 5% (50 ml) and extracted with CH_2Cl_2 (4x70 ml) and dried (MgSO_4). Evaporation of the solvent

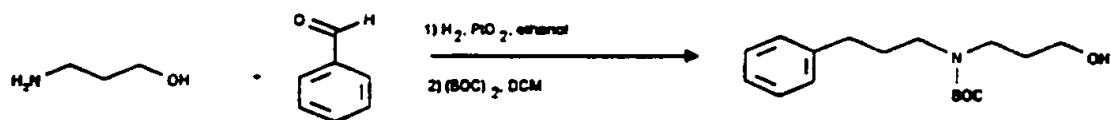
left a residue that was purified on silica gel (1% AcOH, 99% AcOEt) to afford the pure carboxylic acid (125 mg, 32%).



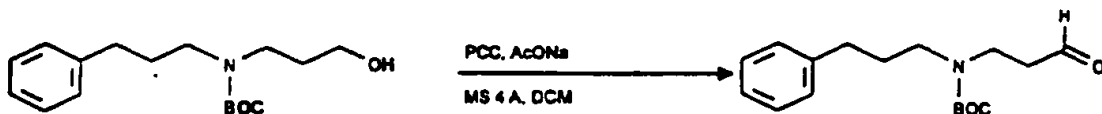
To a solution of the acid (310 mg, 1.06 mmol) in DMF (3 ml) was added successively DIEA (1 ml), the arginine (277 mg, 0.601 mmol) and a solution of BOP (355 mg, 0.841 mmol) in DMF (2 ml). The solution was stirred at room temperature for 20 hours, then poured into water (130 ml), extracted with EtOAc (3x30 ml). The combined organic phases were washed with citric acid 10% (90 ml), NaHCO_3 (s) (90 ml) then brine and dried (Na_2SO_4). Purification of the foam afforded the amide (190 mg, 63%). The amide was dissolved in CH_2Cl_2 (10 ml) and treated at -78°C with BCl_3 1M (2.8 ml). The solution was stirred at room temperature for 2 hours and quenched with dry methanol (3.0 ml) at -78°C . The solution was stirred at room temperature for one hour, then volatiles were evaporated. Purification by HPLC afforded the pure compound A (59.8 mg, fast moving component, one pure isomer) and B (37.4 mg, slow moving component, one pure isomer). *Stereochemistry arbitrarily assigned.

In a like manner, the compounds 13c and 13d were prepared.

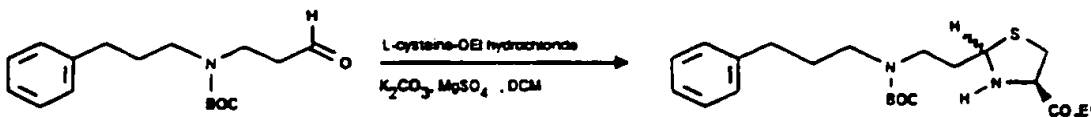
EXAMPLE 5 Synthesis of compounds 12a and 12b



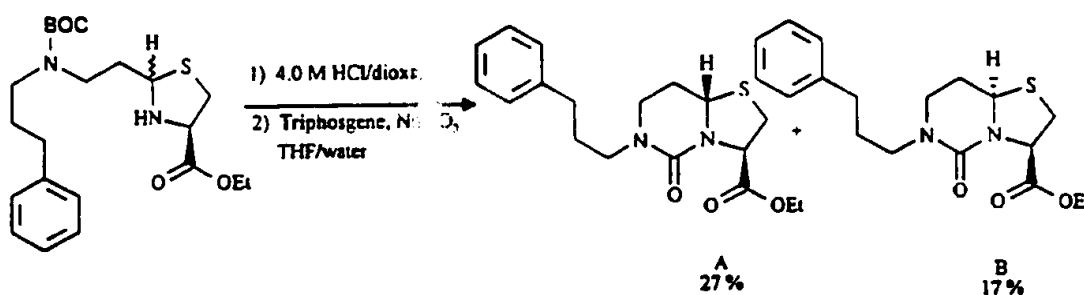
To a solution of the amine (5.0 g, 66.0 mmols) in absolute ethanol (25 ml) was added distilled benzaldehyde (9.0 mL g, 68 mmols). The solution was stirred at room temperature for 10 minutes and PtO_2 (80 mg) was added. The mixture was hydrogenated at 60 psi for 8 hrs at room temperature. The mixture was filtered on celite and volatiles removed. A portion of the crude oil (5.92 g, 30.6 mmols) was dissolved in DCM and treated with $(BOC)_2O$ (6.8 g). The solution was stirred for 15 hrs at room temperature. Volatiles were removed in vacuo and the oil purified on silica gel (EtOAc30%, hexanes 70%) to afford the protected amine (6.40 g; 71%).



To a solution of the alcohol (6.21 g, 21.1 mmols) in DCM (200 ml) was added successively sodium acetate (2.6 g) and powdered M.S 4 A (7.0 g). The mixture was cooled to 0 °C then PCC (6.9 g; 32 mmols) was added. The mixture was stirred at 0 °C for 45 minutes then at room temperature for 1 hour. The mixture was filtered through florisil and washed several times with DCM. Evaporation of the solvent left an oil that was purified on silica gel (EtOAc20%, hexanes 80%) to afford the aldehyde (2.85 g; 46%).



A mixture of the aldehyde (2.71 g, 9.30 mmols), L-cysteine ethyl ester • HCl (2.91 g, 15.7 mmols), potassium carbonate (9 g) and magnesium sulphate (9 g) in CH_2Cl_2 (75 ml) were stirred at room temperature for 17 hours. The mixture was poured into NaHCO_3 (200 ml) and extracted with CH_2Cl_2 (3x200 ml). The combined organic phases were dried (MgSO_4). Purification of the oil on silica gel (20% EtOAc/80% hex) afforded the thioaminal (3.62 g, 92%).

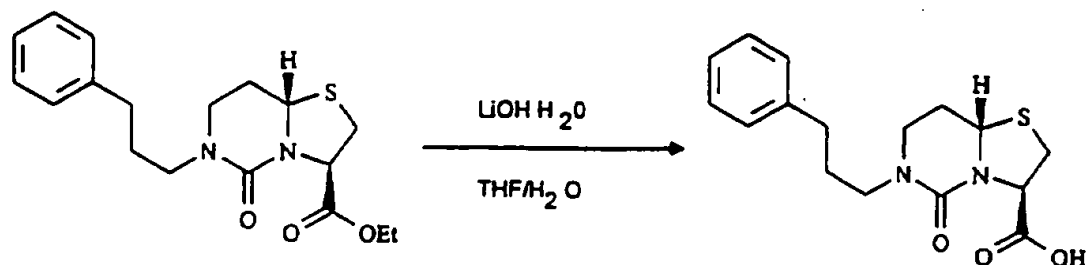


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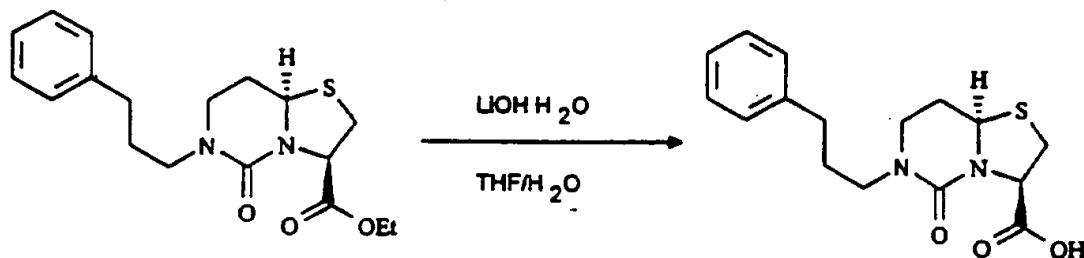
The protected amine (3.2g) dissolved in EtSMe (4 ml) was treated with 4.0 M HCl in dioxane (50 mL) and stirred for 75 minutes. The mixture was poured into a saturated solution of NaHCO_3 (200 ml) and an additional 20 g of NaHCO_3 was added. The aqueous mixture was extracted with EtOAc (3x200 ml) and the combined organic phases were washed (brine), dried (Na_2SO_4). Evaporation of the volatiles left the crude deprotected amine (1.35 g, 97%). The crude amine (1.23 g, 4.17 mmols) dissolved in THF (15 ml) and treated successively with a solution of Na_2CO_3 (885 mg) in water (15 ml) followed by a solution of triphosgene (408 mg, 1.37 mmols). The mixture was stirred at room temperature for 19 hours, then poured into water (60 ml) and extracted with CH_2Cl_2 (4x60 ml). The combined organic phases were washed with HCl 5% (200 ml), NaHCO_3 (200 ml), and dried (MgSO_4). Purification on silica gel (EtOAc 50%, hexanes 50%) afforded the urea A (745 mg, 27%)

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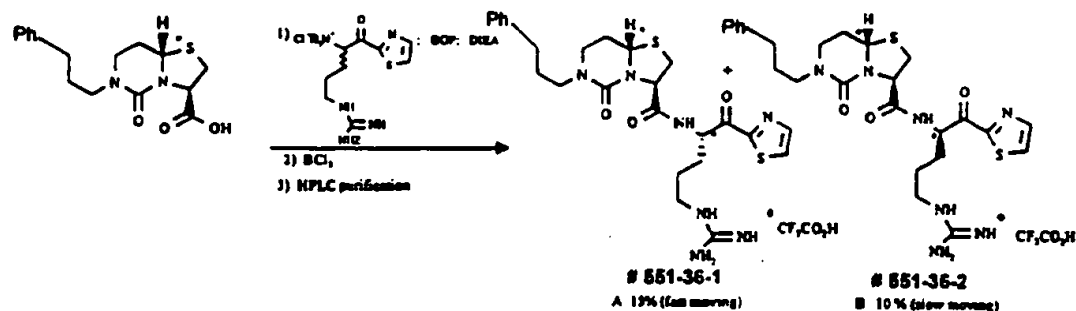
and the urea B (457 mg, 17%). The stereochemistry at the angular position is arbitrarily assigned.



A solution of the ester (698 mg) in THF (10 ml) was treated with LiOH·H₂O (74 mg, 1.8 mmols) in water (10 ml). The solution was stirred at room temperature for 60 minutes then poured into 5% HCl (50 ml) and extracted with CH₂Cl₂ (4x70 ml) and dried (MgSO₄). Evaporation of the solvent left the crude carboxylic acid (614 mg, 96%).



A solution of the ester (418 mg) in THF (10 ml) was treated with LiOH·H₂O (161.6 mg, 3.85 mmols) in H₂O (10 ml). The mixture was stirred at room temperature overnight. The mixture was poured into HCl 5% (50 ml) and extracted with CH₂Cl₂ (4x70 ml) and dried (MgSO₄). Evaporation of the solvent left a residue that was purified on silica gel (1% AcOH, 99% AcOEt) to afford the pure carboxylic acid (221 mg, 57%).



To a solution of the acid (208 mg, 0.647 mmol) in DMF (3 ml) was added successively DIEA (0.5 ml), the arginine (277 mg, 0.601 mmol) and a solution of BOP (355 mg, 0.841 mmol) in DMF (2 ml). The solution was stirred at room temperature for 20 hours, then poured into water (130 ml), extracted with EtOAc (3x30 ml). The combined organic phases were washed with citric acid 10% (90 ml), NaHCO₃(s) (90 ml) then brine and dried (Na₂SO₄). Purification of the foam afforded the amide (190 mg, 63%). The amide was dissolved in CH₂Cl₂ (10 ml) and treated at -78°C with BCl₃ 1M (2.8 ml). The solution was stirred at room temperature for 2 hours and quenched with dry methanol (3.0 ml) at -78°C. The solution was stirred at room temperature for one hour, then volatiles were evaporated. Purification by HPLC afforded the pure compound A (62 mg, fast moving component, one pure isomer) and B (44.4 mg, slow moving component, one pure isomer). *Stereochemistry arbitrarily assigned.

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In a like manner, compounds 12c and 12d were prepared.

EXAMPLE 6 Thrombin Affinity

The affinity of inhibitors for thrombin was measured according to the procedures described in (DiMaio et al, J. Bio. Chem., 1990, 265:21698) Inhibition of amidolytic activity of human

thrombin was measured fluorometrically using Tos-Gly-Pro-Arg-AMC as a fluorogenic substrate in 50 mM Tris-HCl buffer (pH 7.52 at 37°C) containing 0.1 M NaCl and 0.1% poly(ethylene glycol) 8000 at room temperature, and (Szewczuk et al., Biochemistry, 1992 31:9132).

The hydrolysis of the substrate by thrombin was monitored on a Varian-Cary 2000™ spectrophotometer in the fluorescence mode ($\lambda_{ex} = 383$ nm, $\lambda_{em} = 455$ nm) or on a Hitachi F2000™

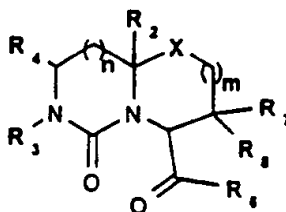
10 fluorescence spectrophotometer ($\lambda_{ex} = 383$ nm, $\lambda_{em} = 455$ nm), and the fluorescent intensity was calibrated using AMC. The reaction reached a steady-state within 3 minutes after mixing thrombin with the substrate and an inhibitor. The steady-state velocity was then measured for a few minutes. The compounds of this invention were also pre-incubated with thrombin for 20 minutes at room temperature before adding the substrate. The steady-state was achieved within 3 min and measured for a few min. The kinetic data (the steady-state velocity at various concentrations of the substrate and the inhibitors) of the
20 competitive inhibition was analyzed using the methods described by Segel (1975). A non-linear regression program, RNLIN in the IMSL library (IMSL, 1987), LMDER in MINPACK library (More et al., 1980) or Microsoft™ Excell™, was used to estimate the kinetic parameters (K_m , V_{max} and K_i).

Table 1

Compound	Ki (nM)
<u>6</u>	80
<u>13a</u>	90
<u>13b</u>	900
<u>13c</u>	500
<u>13d</u>	1000
<u>12c</u>	460
<u>12d</u>	100
<u>12a</u>	40
<u>12b</u>	320

WE CLAIM:

1. A compound of formula (I):



wherein:

X is selected from CH-R₅, O, S, SO, SO₂ and NR, wherein R₅ is hydrogen, C₁₋₆ alkyl optionally interrupted with 1 or 2 heteroatoms; C₆₋₁₆ aryl, C₃₋, cycloalkyl or heterocyclic ring or a hydrophobic group;

R₂ is selected from H, NH₂ and C₁₋₆ alkyl optionally substituted with C₆ aryl, a 6 member heterocycle or a C₃₋₇ cycloalkyl ring;

R₃ and R₄ are independently selected from H; NR₆R₇; C₆₋₁₆ aryl or C₃₋₇ cycloalkyl optionally substituted with C₁₋₆ alkyl; C₁₋₁₆ alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR₆R₇ or a C₆₋₁₆ aryl, heterocycle or C₃₋₇ cycloalkyl group optionally substituted with halogen, hydroxyl, C₁₋₆ alkyl; an amino acid side chain; and a hydrophobic group;

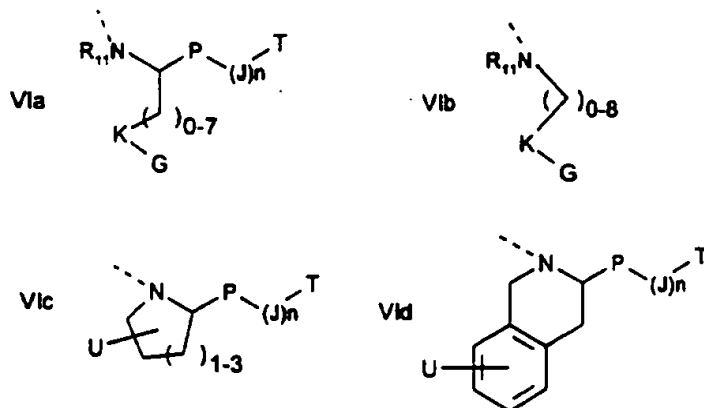
R₆ is a polar amino acid residue, arginyl moiety or an analog or derivative thereof optionally substituted with an amino acid, a peptide or a heterocycle;

R₇ and R₈ are independently hydrogen or C₁₋₆ alkyl;

m is an integer between 0 and 2; and

n is an integer between 0 and 2.

2. A compound according to claim 1, wherein R_6 is one of formula VIa to VIId:



wherein:

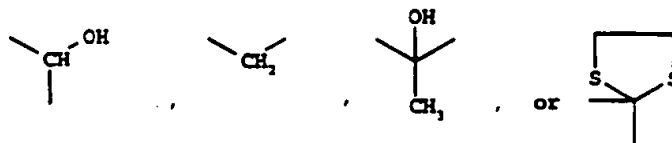
R_{11} is hydrogen or C_{1-6} alkyl;

K is a bond or $-NH-$;

G is C_{1-4} alkoxy; cyano; $-NH_2$; $-CH_2-NH_2$; $-C(NH)-NH_2$; $-NH-C(NH)-NH_2$; $-CH_2-NH-C(NH)-NH_2$; a C_6 cycloalkyl or aryl substituted with cyano, $-NH_2$, $-CH_2-NH_2$, $-C(NH)-NH_2$, $-NH-C(NH)-NH_2$ or $-CH_2-NH-C(NH)-NH_2$; or a 5 or 6 member, saturated or unsaturated heterocycle optionally substituted with cyano, $-NH_2$, $-CH_2-NH_2$, $-C(NH)-NH_2$, $-NH-C(NH)-NH_2$ or $-CH_2-NH-C(NH)-NH_2$;

U is cyano, $-NH_2$, $-C(NH)-NH_2$ or $-NH-C(NH)-NH_2$;

P is a bond, $-C(O)-$ or a bivalent group:

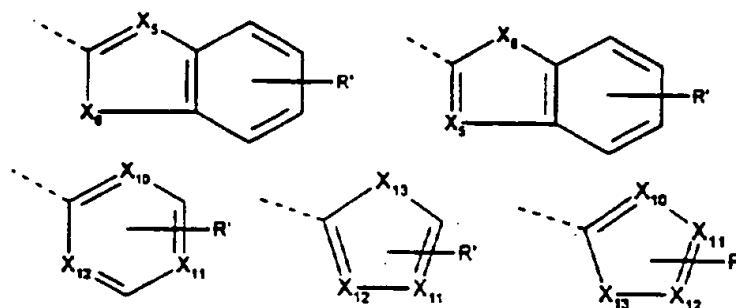


J is C_{1-6} alkylene optionally substituted with OH , NH_2 and C_{1-6} alkyl and optionally interrupted by a heteroatom selected from O , S and N ;

n is 0 or 1; and

T is H, OH, amino, a peptide chain, C₁₋₁₆ alkyl, C₁₋₁₆ alkoxy, C₆₋₂₀ aralkyl, or heterocycle optionally substituted.

3. A compound according to claim 2, wherein T is a heterocycle selected from the group consisting of:



wherein

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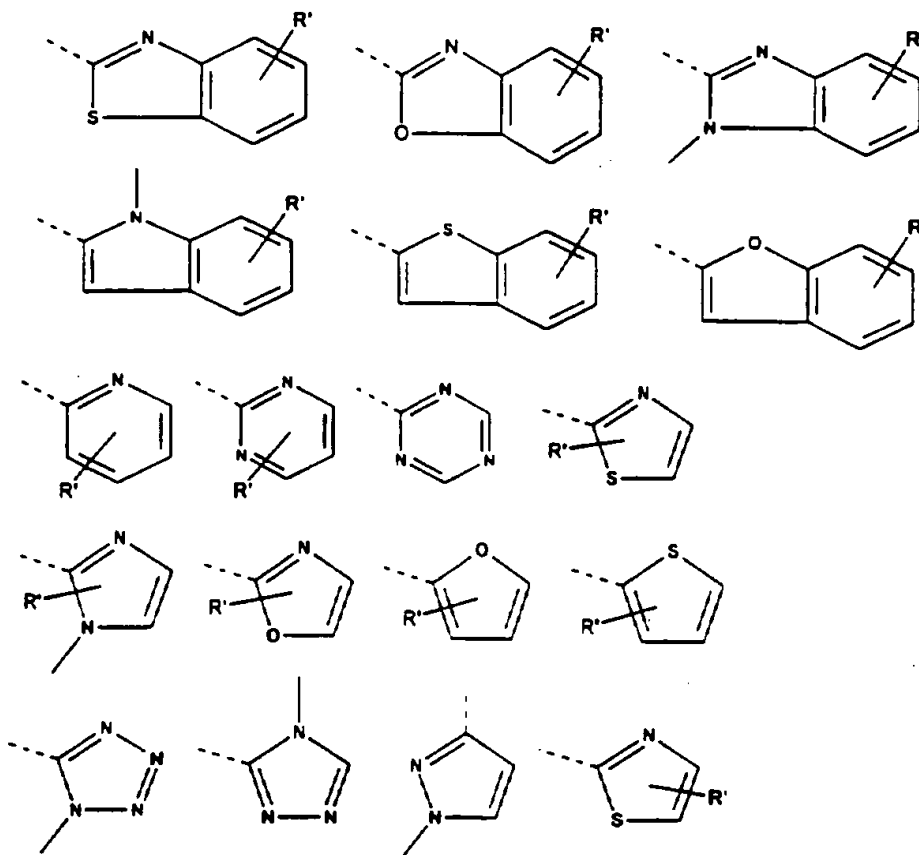
X₅, X₁₀, X₁₁ and X₁₂ are each independently selected from the group consisting of N, or C-X₇, where X₇ is hydrogen, C₁₋₄ alkyl, or C₅₋₈ aryl;

X₆ and X₁₃ are each independently selected from the group consisting of C, O, N, S, N-X₇, or CH-X₇; and

R' is hydrogen, C₁₋₁₆ alkyl optionally carboxyl substituted, carboxyl, -C₀₋₁₆ alkyl-CO₂-C₁₋₁₆ alkyl, C₆₋₂₀ aralkyl, C₃₋₇ cycloalkyl, aryl or an aromatic heterocycle.

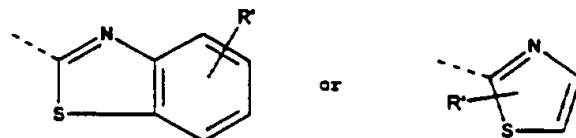
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4. A compound according to claim 3, wherein T is selected from the group consisting of:



wherein R' is hydrogen, C₁₋₁₆ alkyl optionally carboxyl substituted, carboxyl, -C₀₋₁₆ alkyl-CO₂-C₁₋₁₆ alkyl, C₆₋₂₀ aralkyl, C₃₋, cycloalkyl, aryl or an aromatic heterocycle.

5. A compound according to claim 4, wherein T is selected from:



10

wherein R' is hydrogen, C₁₋₁₆ alkyl optionally carboxyl substituted, carboxyl, -C₀₋₁₆ alkyl-CO₂-C₁₋₁₆ alkyl, C₆₋₂₀ aralkyl, C₃₋, cycloalkyl, aryl or an aromatic heterocycle.

6. A compound according to claim 1, wherein one of R₃ and R₄ is a hydrophobic group selected from C₁₋₂₀ alkyl, C₂₋₂₀

alkenyl or C₂₋₂₀ alkynyl optionally interrupted by a carbonyl group, C₆₋₁₆ aryl, C₃₋₇ cycloalkyl, C₆₋₂₀ aralkyl, C₆₋₂₀ cycloalkyl substituted C₁₋₂₀ alkyl, wherein the aliphatic portion is optionally interrupted by a carbonyl group and the ring portion is optionally substituted with C₁₋₆ alkyl; and a hydrophobic amino acid side chain.

7. A compound according to claim 1, wherein R₄ is H.
- 10 8. A compound according to claim 1, wherein R₁ is H.
9. A compound according to claim 1, wherein R₂ is H.
10. A compound according to claim 9, wherein X is S, m is 0 and n is 1.
11. A compound according to claim 9, wherein X is S, m is 0 and n is 0.
- 20 12. A compound according to claim 9, wherein m is 1 and n is 0.
13. A compound according to claim 9, wherein m is 1 and n is 1.
14. A compound according to claim 1, selected from:
6-benzyl-5-oxo-hexahydro-imidazo[5,1-b]thiazole-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide;

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6-benzyl-5-oxo-hexahydro-thiazolo(3,2-c)pyrimidine-3-carboxylic acid (4-guanidino-1-(benzothiazole-2-carbonyl)-butyl)-amide;

6-(para-tBu-phenylmethyl)-5-oxo-hexahydro-imidazo[5,1-b]thiazole-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide;

10

6-(3-phenyl-prop-2-enyl)-5-oxo-hexahydro-imidazo[5,1-b]thiazole-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide;

6-(cyclohexylmethyl)-5-oxo-hexahydro-imidazo[5,1-b]thiazole-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide;

6-(2-trifluoromethyl quinolin-7-yl)-5-oxo-hexahydro-thiazolo(3,2-c)pyrimidine-3-carboxylic acid (4-guanidino-1-(thiazole-2-carbonyl)-butyl)-amide;

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6-phenylpropyl-5-oxo-hexahydro-thiazolo(3,2-c)pyrimidine-3-carboxylic acid (4-guanidino-1-(thiazole-2-carbonyl)-butyl)-amide; and

6-benzyl-5-oxo-hexahydro-thiazolo(3,2-c)pyrimidine-3-carboxylic acid (4-guanidino-1-(thiazole-2-carbonyl)-butyl)-amide.

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15. A method for the treatment or prophylaxis of thrombotic disorders in a mammal, comprising administering to said mammal an effective amount of a compound according to claim 1.

16. A method according to claim 15, wherein said thrombotic disorder is venous thrombosis.
17. A method according to claim 15, wherein said thrombotic disorder is a pulmonary embolism.
18. A method according to claim 15, wherein said thrombotic disorder is arterial thrombosis.
- 10 19. A method according to claim 15, wherein said thrombotic disorder is myocardial infarction.
20. A method according to claim 15, wherein said thrombotic disorder is cerebral infarction.

INTERNATIONAL SEARCH REPORT

National Application No

PCT/CA 96/00318

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D513/04 A61K31/435 //(C07D513/04,277:00,239:00),
(C07D513/04,277:00,235:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TETRAHEDRON, vol. 49, no. 17, 1993, OXFORD GB, pages 3577-3592, XP000576111 U. NAGAI ET AL: "Bicyclic turned dipeptide (BTD) as a beta-turn mimetic; its design, synthesis and incorporation into bioactive peptides" see page 3590 --- -/--	1

☒ Further documents are listed in the continuation of box C.☐ Patent family members are listed in annex.

* Special categories of cited documents:

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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search

19 July 1996

Date of making of the international search report

29. 07. 96

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INTERNATIONAL SEARCH REPORT

National Application No
PCT/CA 96/00318

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 108, no. 9, 29 February 1988 Columbus, Ohio, US; abstract no. 75817d, UKON NAGAI ET AL: "Synthesis of an LH-RH analog with restricted conformation by incorporation of a bicyclic beta-turn dipeptide unit" page 728; XP002008859 see abstract & PEPT. CHEM., vol. 24, 1987, pages 295-298, ---	1
A	CHEMICAL AND PHARMACEUTICAL BULLETIN., vol. 39, no. 3, March 1991, TOKYO JP, pages 584-589, XP000576123 K. KAWASAKI ET AL: "Amino acids and peptides. XIII. Synthesis studies on N-terminal tripeptide amide analogs of fibrin alpha-chain" see page 584 - page 585 -----	1,15